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.

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Exploring the development of the gut-brain axis through the nodose ganglion projections

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The enteric nervous system (ENS) controls gastrointestinal (GI) motility to move the food bolus, nutrient absorption, satiety and contributes to the intestinal barrier protective role, while probably having many additional and yet unknown roles. Remarkably, a direct connection was discovered between nodose neurons, forming a pair of sensory ganglia physically affixed to the vagus nerve at the brainstem level and specialized epithelial cells sensing gut stimuli, the enteroendocrine cells (now renamed neuropod cells). The pseudo-unipolar nodose neurons derive from the branchial arches. Their central axon branch connects the nucleus of the solitary tract in the hindbrain while their peripheral branch projects onto target organs, mainly the heart and the gut. Yet, very little is known on the formation of this gut-brain direct synaptic connection. We investigated the development of nodose peripheral projections using the chicken embryo model. The placodes were unilaterally electroporated with an integrative vector coding for the GFP. Embryos were harvested at different timepoints and immunolabeled with Tuj1 antibody to trace the two nodose tracts. Surprisingly, we observed that nodose axon projections have an ipsilateral and commissural organization. The navigating left and right axon tracts converge to form a unique bundle passing through the thoracic-abdominal subdivision, then diverge into two left and right tracts having ipsilateral and contralateral components, to encompass the gizzard and course towards the gut. At later stages, we observed the nodose axons diving into the GI thickness towards the epithelial surface. Next, to gain insights into the mechanisms controlling the pathfinding of nodose axons, we took a single nucleus RNA sequencing approach of the nodose ganglia, focusing on two stages that temporally correlate the early nodose axon chiasm and the navigation towards the target neuropods within the gut.
Our study will provide novel information on the developmental processes and molecular pathways implicated in the wiring of the gut-brain connection that may have translational potential for the clinic in the context of paediatric diseases affecting gut functions.

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Title : Dynamics of axon guidance transcriptional programs directing early differentiation of vagal neural crest-derived enteric neurons

Authors
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The architecture of enteric neuronal circuits is organised in a complex honeycomb network that spans the entire gastrointestinal (GI) tract. The different enteric neuron subtypes are clustered in repeating ganglia, and their axons form proper stereotyped patterns. The migration of the vagal neural crest, which gives rise to most enteric neurons, has been extensively studied. In contrast, the mechanisms underlying the navigation of enteric axon populations remain poorly characterised. Furthermore, it is unclear whether their alterations contribute to developmental GI motility disorders. We investigated the molecular axon guidance programmes that control enteric axon trajectories by combining experimental manipulations in the chick embryo model with 3D imaging and transcriptomic approaches, focusing on stages following colonisation of the gut by vagal neural cell crest (VNCC) precursors. First, we found a highly dynamic development of the network from E4 to E6. At E5, most axons show a rostro-caudal orientation. At E6, the complexity of the axonal network increases with the emergence of circumferential trajectories. Second, to capture the transcriptional programmes that control these axonal orientations, we performed single nucleus transcriptome analysis at these two stages. We characterised the dynamics of transcriptional landscapes and axon guidance receptor gene sets differentially expressed by axon-forming neurons. Interestingly, the transcriptional trajectories were consistent with those reported in human embryonic gut scRNAseq datasets, supporting conservation of the developmental dynamics of ENS differentiation. Third, we selected two genes for functional studies, DSCAM, a well-known molecule implicated in Hirschsprung disease, and ISLR2, whose functions in ENS formation and disease are poorly documented. We developed a paradigm combining HCR RNA-FISH, immunofluorescence labelling and light sheet microscopy and confirmed the expression of both candidates in the differentiating ENS. We established conditions of ex vivo whole gut cultures recapitulating in vivo E4 to E6 axon patterns as well as in vivo ShRNA approaches to manipulate DSCAM and ISLR2 signalling. Our results provide promising evidence for a role of these genes during ENS axon differentiation and provide novel entry points for studies of paediatric intestinal motility disorders.

Molecular mechanisms underlying *in vivo* reprogramming of glial cells into GABAergic induced neurons in a rodent model of mesio-temporal lobe epilepsy

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Glia-to-neuron reprogramming has emerged as a neuron-replacement strategy in various neurological disorders. We have recently shown, in a mouse model of Mesio-Temporal Lobe Epilepsy (MTLE) that resident glia proliferating in the epileptic hippocampus can be efficiently reprogrammed into GABAergic induced neurons (iNs) able to functionally integrate into epileptic networks and reduce seizures (Lentini et al, 2021). While these are exciting findings, the mechanisms underlying glia-to-neuron conversion *in vivo* are still poorly understood.

To tackle this question, we performed transcriptomic profiling using single-nuclei RNA sequencing of *in vivo* glia-to-neuron reprogramming within the hippocampus of MTLE mice. Nuclei extraction was performed at 4 days post-infection with a retrovirus encoding Ascl1 and Dlx2, along with a nuclear GFP reporter, followed by FACS sorting of GFP+ nuclei and encapsulation for 10x sequencing. Clustering revealed the presence of four distinct clusters composed respectively of microglia, astrocytes, NG2 glia and GABAergic iNs. GABAergic iNs were characterized by the overexpression of several neuronal as well as GABAergic markers. Strikingly, they also still expressed at low levels some features of NG2 glia, suggesting an oligodendroglial origin for those iNs. This was confirmed by pseudotime ordering that highlighted a reprogramming trajectory from NG2 glia to GABAergic iNs. Gene expression along the pseudotime suggested a temporal sequence in which acquisition of neuronal features and GABAergic identity indeed occurred before complete loss of the NG2 glia identity. Astrocytes also seemed capable of reprogramming within the epileptic hippocampus, as a subset of them exhibited expression of neuronal and GABAergic markers. Interestingly, differential gene expression analysis highlighted a small degree of transcriptional similarity between GABAergic iNs and reprogrammed astrocytes, suggesting that they might share common reprogramming processes. Lastly, microglia seemed refractory to Ascl1/Dlx2-mediated conversion. Those results suggest that diverse glial cell-types might show distinct reprogramming competence but that reprogramming of cells of different glial origin into GABAergic iNs might involve similar mechanisms.

Further research will be performed to extend this analysis to other time-points along the reprogramming trajectory, allowing to decipher the full transcriptional program underlying *in vivo* glia-to interneuron reprogramming in the injured hippocampus. Those results will prove essential to unravel the principles that guide reprogramming and identify critical steps that can be manipulated to enhance both efficiency and accuracy of glia reprogramming into GABAergic iNs.

The sweet side of glia-to-neuron reprogramming

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Our adult mammalian CNS lacks intrinsic regenerative capacity to replace lost neurons and induce functional recovery after 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 transcription 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 reactive glia into GABAergic iNs that integrate within epileptic networks and reduce chronic seizure activity, thus uncovering glia-to-iN reprogramming as a potential disease-modifying strategy to control drug-resistant seizures (Lentini *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, epigenetic landscapes, and metabolic status. We here hypothesized that O-GlcNAcylation –a dynamic form of protein glycosylation which has emerged as critical regulator of numerous cell processes– could play a key role in lineage reprogramming by controlling epigenetic regulations, rewiring of TF networks, and the metabolic shift. O-GlcNAcylation 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. Interestingly, 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-GlcNAcylation play a role during Ascl1/Dlx2-driven reprogramming, we inhibited OGT enzymatic activity using a specific pharmacological inhibitor in astrocytes undergoing neuronal conversion. Strikingly, we observed a dramatic reduction of the number of iNs derived from astrocyte reprogramming compared to controls. Moreover, iNs generated upon OGT inhibition displayed a significantly less complex neuronal architecture compared to control iNs, as revealed by reduced dendritic length and intersection numbers. We next hypothesized that this reduction in the number of iNs could result from decreased cell division during reprogramming or impaired cell survival of iNs upon OGT inhibition. To test this hypothesis, we performed continuous time-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 inhibition, 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 inhibition observed in Ascl1/Dlx2-mediated reprogramming of astrocytes into GABAergic iNs would also be observed during their conversion into glutamatergic iNs. To our surprise, inhibition of OGT during Neurog2-induced reprogramming of the same astrocyte population increased neuronal reprogramming efficiency and had no apparent impact on survival of iNs. Taken together, our results uncover OGT/O-GlcNAcylation as a key mediator during astrocyte-to-neuron reprogramming.

Title: Alterations of cortical circuits in mice following premature brain injuries

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Cortical circuits are built at perinatal times and gradually refined in an activity-dependent manner during a so-called postnatal period of critical plasticity. Although lesions of the central nervous system (CNS) happening during this period recover better than those occurring later in life, they are often associated with long-term behavioral deficits. This suggests that neuronal circuits rewiring, in particular within the cortex, may either be incomplete or inappropriate.
We used chronic perinatal hypoxia, a mouse model of very premature birth. We confirmed that chronic hypoxia induced a decrease in cortical thickness frequently observed in very preterm babies, which rapidly recovered 8 days later. Despite of this macroscopic anatomical recovery, behavioral testing revealed altered social behavior in mice exposed to chronic hypoxia, which amplified with age. We next performed single-nuclei transcriptomic analysis of the cortex at short (P11) and long (P45) timepoints following hypoxia, which revealed persistent transcriptional changes within neurons, including of genes involved in synaptic function and mitochondrial metabolism. Further, cell-cell communication analysis using NeuronChat supported an overall increase of connectivity within the cortex of hypoxic mice. Histological analysis using anterograde and retrograde tracing as well as mitochondrial labelling confirmed these results by showing long term changes in projection/connectivity and mitochondrial content of cortical neurons following hypoxia.
Altogether, our results unravel how brain lesions happening early in life, have long term consequences on cortical neuron maturation and homeostasis, which may contribute to the observed behaviors defects appearing later in life.

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.

Role of TMEDs proteins in Acetylcholine Receptors Biosynthesis

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Acetylcholine Receptors (AChRs) mediate synaptic transmission at neuromuscular junctions (NMJ) and support various functions in the central nervous system. AChRs are composed by five subunits. Assembling AChRs is challenging for the cell machinery and different neuromuscular diseases are caused by decreased AChR expression. AChR biosynthesis is slow and inefficient and many factors involved in this process remain uncharacterized. To shed light on the complexity of AChRs biogenesis, we performed a genetic screen in *Caenorhabditis elegans* for decreased AChR expression and found that TMED-3, the ortholog of human TMED7, and SEL-9, the ortholog of human TMED2, are important regulators of AChRs.

TMED-3 and SEL-9 belong to the TMED (transmembrane emp24 protein transport domain containing) protein family, which is involved in ER to Golgi trafficking. TMEDs contain a Golgi dynamics (GOLD) domain that mediates the interaction with cargo proteins, coiled-coil domains responsible for dimerization, a transmembrane region and a cytosolic tail with COPII-binding di-phenylalanine motif (FF-motif). ER-Golgi transition of proteins destined for secretion requires COPs recruitment and TMEDs act as adaptors for cargos lacking COP-binding domain. We are characterizing the function of TMEDs in *C. elegans* and our preliminary results suggest that both SEL-9 and TMED-3 are required for the anterograde transport of L-AChR in *C. elegans* muscle cells.

Studying the dynamics of neuromuscular junction proteins

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The neuromuscular junction in *C. elegans* consists of alternating excitatory (cholinergic) and inhibitory (GABAergic) synapses along nerve cords. Muscle cells thus receive two types of afferences and must localize the different neurotransmitter receptors in front of the corresponding presynaptic boutons to insure correct neurotransmission. At the level of the muscle cell membrane, two types of cholinergic receptors (N-AChRs and L-AchRs) and one type of GABAergic receptors ($GABA_A$Rs) are clustered by specific intracellular and extracellular scaffolds. N-AChRs are the ortholog of α7 nicotinic receptors in mammals and are formed by a homo-pentamer of ACR-16 subunits. L-AChRs possess three α subunits (LEV-8/ACR-8, UNC-38 and UNC-63) and two non-α subunits (LEV-1 and UNC-29) and are sensitive to levamisole, an anthelmintic drug. These clusters of receptors are then localized by different extracellular synaptic organisers: Punctin/MADD-4 and CLE-1. Punctin is the ortholog of ADAMTSL3, a glycoprotein that belongs to the ADAMTS-like family. CLE-1 is the ortholog of collagens XV/XVIII, two multiplexin collagens that form a triple helix of collagen as well as possess heparan and/or chondroitin sulfate chains.

To better understand how these proteins are organised and interact together over time, it is essential to determine their dynamics. To do so, I have recently performed Fluorescence Recovery After Photobleaching (FRAP) on the three types of receptors, Punctin and CLE-1 using knock-in strains. I have also performed photoconversion to follow the renewal rate of Punctin.

FRAP experiments showed that extracellular matrix proteins are very stable at the neuromuscular junction, with very little recovery within the hour after photobleaching. These results suggest that Punctin and CLE-1 could establish very strong interactions within the extracellular matrix of the synapse that may limit their diffusion in the extracellular space. In contrast, the receptors showed recovery within the first 15 min after photobleaching. This recovery then reached a plateau, highlighting the presence of both mobile and immobile fractions of receptors. The different receptors showed specific rates of recovery and mobile fractions.

Finally, photoconversion of Punctin in *C. elegans* larvae showed that there is a complete renewal of Punctin after 24h. We are currently building knock-in strains with photoconvertible proteins tagged to each of our protein of interest in order to systematically follow the population of photoconverted and non-photoconverted proteins at *C. elegans* neuromuscular junctions.

This study shows that the dynamic of neuromuscular junction proteins varies according to the type of protein.

Searching for new regulators at *C. elegans* synapses

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ACR-16 is the *Caenorhabditis elegans* ortholog of the α7 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 extra- and 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.

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.

Amarine Chancel, PhD de l'équipe Sleep au CRNL.

Background: Hypothalamus (hyp) regulates many physiological functions. One of these most studied neuronal populations is the Orexin neurons active during waking (W). Besides, our team has shown in rodents there are many cFos-immunopositive cells within the lateral hypothalamus (LH), zona incerta and perifornical area, after a homeostatic Paradoxical Sleep (PS) rebound. Many neurons express either melanin-concentrating-hormone (MCH), GAD2 or Lim homeobox6 (Lhx6). We want to determine the percentage of neurons activated during W and PS which are expressing MCH, Lhx6 and Orex, to determine the proportion of neurons activated during W and PS in the different hypothalamic nuclei which are not chemogenetically identified.
Methods: Thanks to the transgenic mouse TRAP2-red, we can map in the same animal the neurons activated during W and those during PS rebound, which allows to show differential topography within hyp. We used 4 males implanted with EEG/EMG. They were kept awake during 4h and were IP injected by 4-hydroxytamoxifen (50mg/kg) after the first 2h. One week later, they were submitted to a 48h automatic PS deprivation and then allowed to recover for 2h before sacrifice. Sections were treated for the immunofluorescent detection of cFos, orex, Lhx6 and MCH. They were scanned to map the distribution of tdtomato, cFos, MCH, Lhx6, Orex and double- and triple-labeled neurons and were counted.
Results: MCH neurons are activated during PS rebound but not W, while surprisingly Orex neurons are activated during the two conditions. In the caudal LH, two MCH subpopulations might be distinguished, one is ventral/medial while the other is dorsal. In addition, our results indicate that in most of the hypothalamic structures many neurons activated during W and PS rebound aren’t containing Orex, Lhx6 and MCH, indicating that most of the hypothalamic neurons activated during PS and W have not yet been studied. Finally, certain structures are specifically implicated in W or PS while others like the LH or DMH, seem to play a role in both states.
Conclusions: Our results indicate that LH contains other unknown populations of neurons active during W and PS. Our aim in the future is to identify specific markers for these neurons to study their function.

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.

Repurposing FDA-approved drugs to promote myelin repair following early brain injuries

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Postnatal hypoxia affects infants born prematurely, leading to increase risks of psychiatric disorders and lower cognitive performance later in life. Among other cell types, postnatal hypoxia affects oligodendrocytes that play an important role in axon myelination. Identifying molecules that can promote oligodendrocyte production by endogenous neural stem cells as well as their maturation is therefore of major interest to reduce the long term impact of hypoxia on brain functioning. Based on a pharmacogenomic analysis (Azim et al., 2017, Hure et al, in revision), we have identified and patented 2 small molecules that promote oligodendrocyte production and maturation in various contexts.

We developed a new approach for brain wide automatic quantification of oligodendrocytes numbers and maturation from serial brain sections. We first applied this approach to analyze the effects of early postnatal hypoxia on oligodendrocytes throughout brain regions, to identify those most affected. We complemented this work by analyzing the regenerative potential of the 2 small molecules in this model of very premature birth.

Our results reveal a region-specific blockade of oligodendrocytes maturation as well as different capacity of the two small molecules to promote myelination following postnatal hypoxia.

The importance of the retinotopic subdivisions of area V1 in shaping the macaque connectome.

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The spatial embedding of the cortical connectome ensures that inter-areal connection strength is largely determined by distance. A flat map of macaque area V1 show that the areal neighborhoods of the far periphery upper and lower visual field representations are highly distinct from each other and from that of the fovea, predicting that they exhibit distinct connectivity profiles. Tracer injections in upper and lower visual fields in areas V1 and V2 revealed different connectivity profiles at different eccentricities and showed 15 projections not found after central injections. Connection strengths of the majority of projections differ significantly with eccentricity in a systematic fashion with respect to distance and origin; whereas projections to central and upper visual field representations are significantly stronger from ventral stream areas, peripheral lower field projections are stronger from the dorsal stream. These differences in the feedback to area V1 and V2 are echoed by differences in their feedforward projections. The Voronoi portioning and the shortest pathlength analysis revealed that trees rooted in the peripheral lower and upper field as well as the fovea representations of V1 reach different cortical areas and make distinct clusters. Projection differences in upper and lower fields of V1 and V2 are discussed with respect to their cognitive and perceptual roles. In addition, analysis based on published single cell spatial transcriptome data shows differential gene expression across eccentricity of V1 and V2. Area V1 is unique in having a highly distinctive cytoarchitecture and sharply defined border and yet it is imperative to consider the retinotopic subdivisions. These findings argue in favor of connectomes being not based on Broadman areas and instead future connectomes and large-scale models need to be grounded in a far more fine-grained parcellation of the cortex than is the case for existing models.

Exploring the hub-function of the primate claustrum ensuing orchestration of inter-areal processing

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Abstract: The wide-spread connectivity of the claustrum with the cortex has suggested that it is involved in higher-cognitive functions. However, in mouse recent findings suggest a topographical organization with the cortex and a sensory regionalization of the claustrum. Our earlier work reports important differences in the organizational principals of mouse and primate cortical connectivity. Hence, we have undertaken extensive examination of the projections between claustrum and cortex in macaque using retrograde tracing. Surprisingly, we find that these connections do not obey the exponential distance rule, which is ubiquitous in the cortical network, allowing claustrum to be strongly connected to all neocortical areas. Graph theoretic analysis of these findings show that the claustrum has very high centrality values and that it constitutes the unique hub of the cortex. These results suggest that the spatial embedding of the primate claustrum allows it to play a privileged role in facilitating the orchestration of rapid changes of brain state which we are currently exploring in non-human primate using multisite single unit recording simultaneously across the cortex and in the claustrum.

Subcortical and cortical inputs to anterior insula and claustrum in macaque and mouse suggest possible species-specific implications for the role of interoceptive inference in consciousness

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Interoception refers to the sensation, perception, and metacognition of the visceral cycles that govern an agent's homeostasis, allostasis, and ultimately its survival. It has been proposed that interoceptive inference provides a neural mechanism that supports consciousness [(1)]. The anterior insula cortex (AIC) is a key hub for processing visceral information, and several studies show that AIC is linked to the regulation of both interoception and attention [(2)]. The claustrum is a thin sheet-like structure located in the white matter immediately beneath the insula cortex. It maintains extensive connections with cortical areas and is believed to integrate information from numerous sources and also to be involved in attention and sleep [(3)].

We investigated the cortical and subcortical inputs to the AIC and claustrum in macaque by injecting retrograde tracer in these two regions [(4)]. The results showed that (1) the subcortical projections to AIC are more widely spread than to claustrum (118 out of 199 structures project to AIC, 81 structures project to claustrum). (2) Claustrum receives projections from more cortical areas than does AIC (92 out of 114 areas project to claustrum, 51 areas project to AIC). (3) unlike most cortical areas, where 80% of connections are local, in claustrum only 10% of connections are local [(5)]. (4) Claustrum and AIC are heavily inter-connected in both directions. The connectivity of macaque AIC and claustrum were compared with the connectivity of mouse

AIC [6] and claustrum [7] and found to be surprisingly different. Compared to mouse, in macaque the cumulative weight of inputs from subcortical structures to AIC and claustrum is considerably less (macaque: 10% for AIC and less than 2% for claustrum; mouse: 50% for AIC and 40% for claustrum;). However, compared to mouse, in macaque there are significantly more subcortical source structures projecting to the claustrum (26 out of 206 in mouse, 81 out of 199 in macaque).

These results enrich our understanding of the AIC and claustrum's connectivity and provide insight of their distinct but likely cooperative roles in interoceptive inference, which may however differ significantly in mouse and macaque.

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Neuro-Day Abstract (08/02/2024)

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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Abstract (393 words)

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.

NX210c peptide: a drug candidate to repair the BBB in neurological disorders

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Abstract

BBB dysfunction is likely a disease-driving feature of several neurological disorders, including PD, ALS and MS, yet today no treatment exists to repair the BBB. Here, we screened the effect of a subcommissural organ-spondin-derived peptide (NX210c), known to promote functional recovery in several models of neurological disorders, on BBB integrity *in vitro* and *in vivo* including in healthy elderly volunteers (HEVs).

In vitro, bEnd.3 endothelial cell (EC) monolayers and two different primary human BBBs containing EC, astrocytes and pericytes, in static and microfluidic conditions, were treated with NX210c (1-100 µM), or its vehicle (water). NX210c induced a transient increase in occludin protein expression after 24h treatment (+37% at 100 µM; western-blot) in mouse EC. Claudin-5 protein expression was also increased after 24h (+43% at 100 µM) and 72h (immunocytochemistry). Accordingly, NX210c decreased the permeability of EC by half to a 40-kDa-FITC Dextran and increased transendothelial electrical resistance (TEER). In the human static BBB model, NX210c increased the TEER by 30% at 100 µM after 3 and 5 days. NX210c also increased TEER in the human 3D dynamic BBB model at 100 µM after 4h, which was associated with a reduced permeability to a 4-kDa-FITC Dextran.

In vivo, young and old mice (3- and 21-month-old, respectively) were treated intraperitoneally with NX210c at 10 mg/kg or its vehicle for 5 days once a day and their brains collected at day 6 to perform immunohistochemistry in the cortex and hippocampus. NX210c restored aging-induced reduction of tight junction levels in the brain (+24% and +19% for claudin-5 and occludin respectively, compared to untreated old mice in the hippocampus).

In a phase 1b randomized, double-blind, placebo-controlled, multiple ascending dose study, two cohorts of 15 HEVs were planned to receive NX210c treatment at 5 or 10 mg/kg or its vehicle (4:1 ratio; 2 sentinels/cohort) intravenously 3×/week for 4 weeks. Safety and tolerability were evaluated as the primary objectives and blood pharmacokinetics as the secondary objective. Exploratory objectives assessed pharmacodynamic parameters including plasma and CSF biomarkers of BBB permeability alterations. NX210c was safe and well tolerated by HEVs. Furthermore, we observed positive signals of BBB repair, including a significant reduction overtime of the release of claudin-5 in the plasma in HEVs treated with NX210c.

By repairing the BBB, NX210c may represent a disease-modifying treatment for several neurological disorders which will in turn reduce neurodegenerative processes and promote functional recovery.

A zebrafish model of Autosomal Recessive Cerebellar Ataxia 2 for drug discovery and phenotype prediction

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Autosomal recessive cerebellar ataxia type 2 (ARCA2) leads to disabling symptoms such as ataxia, seizures, spasticity, and cognitive impairments. It is caused by a loss of function mutation in the COQ8A gene that codes for the ATPase COQ8A, a regulatory component of Coenzyme Q10 (CoQ10) biosynthesis. CoQ10 plays a critical role in various metabolic pathways, particularly within mitochondria where it serves as an electron carrier during oxidative phosphorylation, and acts as an important antioxidant. Therefore, ARCA2 disease is thought to be a consequence of CoQ10 deficiency, but due to its inability to cross the blood-brain-barrier, CoQ10 supplementation has been unsuccessful as a therapeutic strategy. [1-2] While mouse models have helped understand the role of COQ8A in CoQ10 biosynthesis, they are impractical for screening efforts aimed at identifying novel potential therapeutic compounds. Therefore, we are developing a zebrafish model for ARCA2 aimed at such high-throughput analyses. Zebrafish has proven to be useful for modelling human neurological conditions, and zebrafish models of ataxia have successfully recapitulated the phenotypic manifestations of the disease. [3] Zebrafish possess two genes homologous to mammalian Coq8a: coq8aa and coq8ab, with the former showing the highest degree of homology to the human gene. [4] Using CRISPR/Cas9 mutagenesis, we have generated coq8aa and coq8ab mutant alleles, and we will present our current results on phenotyping these single and double mutant lines for behavioural, neural activity and neuroanatomical phenotypes.

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Long term olfactory exposure to CO2 increases interneurons-astrocytes structural connectivity in Drosophila antennal lobe

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Critical periods (CP) are specific temporal windows of increased plasticity occurring during development, allowing adjustments of genetically encoded neural circuits in response to experience. In mammals and insects alike, interactions between glial cells and neurons have been shown to play a central role in CP, but the underlying mechanisms are poorly described. In the Drosophila primary olfactory system, chronic exposure to CO2 leads to long-term habituation (LTH), with a CP limited to early adult life. This LTH results in a persistent increase in the volume of the CO2-specific glomerulus (V glomerulus) and reduced behavioral responses to this odor, due in part to enhanced inhibition by GABAergic local interneurons (LN). However, glial cells involvement in these processes remains to be investigated. We report here numerous contacts between LN presynapses and astrocyte cell membranes in the V glomerulus using the GFP Reconstitution Across Synaptic Partners (GRASP) technique. In contrast, much fewer contacts were observed between LN presynapses and ensheathing glia, another cell type that envelops the glomerulus. Furthermore, we find that CO2 exposure induces an increase in GRASP-labeled contacts, particularly between LN presynapses and astrocyte membranes in the V glomerulus, but also in VM6, in the vicinity of V. The CO2-induced increase in the V glomerulus volume was blocked in flies with LN-astrocytes GRASP-labeled contacts, which may be a side effect of GRASP expression. Thus, our results show that CO2 exposure induces an increase in structural connectivity between LN presynapses and astrocytic membranes, suggesting that LTH increases interaction between these cells.

Nociceptors clock genes regulate excitability and pain-related behavior in a time and sex-dependant manner

Aurélie Brécier, Courtney Bannerman, Amanda Zacharias & Nader Ghasemlou

Recent studies have unravelled a daily rhythm of thermal and mechanical sensitivity in humans and mice, suggesting a circadian control of nociception. However, the mechanisms underlying this phenomenon remain unclear. While nociceptive information is primarily transduced by the sensory neurons of the dorsal root ganglia (DRG), also called nociceptors, a link between the activity of DRG neurons and the circadian regulation of nociception has never been established. We propose that circadian rhythms control the excitability of DRG sensory neurons and nociception. RT-qPCR analysis revealed a rhythmic and sex-dependent expression of the core clock genes in mice DRG. Whole-cell recordings from intact DRGs revealed an increased excitability of nociceptors at ZT2 (2h after lights on) compared to ZT14 (2h after lights off) in male mice but not in females. The conditional depletion of the master clock gene, Bmal1, in nociceptors, reduced the increased excitability observed in male sensory neurons at ZT2 and prevented the circadian control of thermal heat sensitivity in male mice, suggesting a cell-autonomous mechanism. RNA-sequencing and voltage-clamp data reported a lower expression and activity of the chloride channel Clcn2 at ZT2 in male mice DRG solely. The conditional depletion of Bmal1 modified the expression of Clcn2 at the DRG level, suggesting a pivotal role of chloride channels in the daily control of excitability and pain-related behavior. Overall, our study proposes that molecular clock modify the excitability level of nociceptors and thermal sensitivity in a time and sex-dependent manner through the circadian expression of chloride channels.

Sacha SECHI, PhD de l'équipe BOULIN à MELIS.

Small-conductance Ca^{2+}-activated K+ channels, commonly known as SK channels, are encoded in humans by the KCNN gene family and are widely expressed in the brain. These channels are highly conserved among vertebrates and invertebrates, and they play a role in afterhyperpolarization following action potentials and regulate the firing frequency of neurons. Mutations in *KCNN2* and *KCNN3* lead to two rare human diseases: NEDMAB (Neurodevelopmental Disorder With or Without Variable Movement or Behavioral Abnormalities) and ZLS3 (Zimmermann-Laband Syndrome 3).
ZLS3 patients harbor missense mutations that increase SK3 channel activity. Conversely, a cohort of fourteen unrelated *KCNN2* patients carries missense mutations that were shown to eliminate channel function by electrophysiological studies. These patients share characteristics such as motor and language developmental delays, intellectual disability, movement disorders, cerebellar ataxia, autistic features, and epilepsy.
To investigate the impact of patient-specific variants, we used CRISPR/Cas9 gene editing to introduce nine human mutations into the *C. elegans* orthologue, *kcnl-1*, that exhibits sequence similarities of more than 50% with KCNN2 and KCNN3. The KCNL-1 channel regulates the excitability of neurons and muscles within the worm's egg-laying system, which constitutes a well-established model circuit for studying neuronal excitability.
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A Deep Learning video-based pipeline for primate action recognition and classification

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Traditional methods for analysis and behavioral tracking in neuroscientific studies involving video-based ethological recordings require costly, laborious, and time consuming manual annotations and labeling by domain experts. In recent years the explosion of modern deep neural network architectures, together with statistical Machine Learning methods, have led to a variety of frameworks and computational solutions that promise to revolutionize the field and allow for greater flexibility and complexity in experimental design and behavioral analysis.

In the present work, as part of the development of a neuroethological lab integrating wireless neural recording and videotracking of freely moving monkeys, we leverage the recent advancements in Deep Learning methods for video-based action recognition, in order to streamline the process of behavioral analysis of macaque recordings.

Our methodology is based on transfer learning applied to state-of-the-art video understanding deep neural network architectures. This approach allows us to overcome the limitations of a relatively low volume of manually labeled data by using a backbone network trained on vast quantities of human data. We then fine-tune the network with highly curated video dataset to recognize non-human primate behavior.

At first a primate recognizer model is used to track individuals and guide the preprocessing of video frames. Afterwards, the video is sampled and evaluated by an efficient temporal-shift deep neural network, trained on short video segments of a couple of free moving macaques, labeled into behavioral categories.

Results demonstrate the effectiveness of our approach and suggest that it has the potential to become a promising tool for systematic behavioral analysis.Furthermore, current work is focusing on incorporating data derived from a multi-animal pose estimation model to strengthen the accuracy, robustness and flexibility of the video-based behavior identification model.

Neuro-Day Abstract (08/02/2024)

WAY-208466, a striatal 5-HT6 receptor agonist, increases food motivation in primates: a preclinical study combining PET imaging and a food intake task opening perspectives in *Anorexia nervosa*.

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Abstract (328 words)

Anorexia nervosa (AN) is a major eating disorder with frequent comorbidities such as anxiety and depression. Unlike isolated anxiety and depression, selective serotonin reuptake inhibitor (SSRI) treatments have not been shown to be an effective aid to re-nutrition in the restrictive subtype (AN-R). The 5-HT_6 receptor (5-HT_6R) is highly expressed in the anterior striatum, a subcortical region known to be involved in food intake and anxiety-related behaviors in non-human primates (NHP), as well as in maladaptive choices in AN-R patients. Preclinical rodent studies have shown the anxiolytic and orexigenic properties of WAY-208466, a selective 5-HT_6R agonist. Thus, we hypothesized that this agent could increase food motivation and decrease anxiety-related behaviors by influencing the activity of the cortico-basal ganglia circuits, including the anterior striatum. This study in NHP aimed, firstly, to determine the potential of WAY-20846 intramuscular injections to increase food intake and decrease anxiety-like behaviors. We tested both sub-acute (0.1 mg/kg) and sub-chronic administration (0.03 and 0.1 mg/kg) in a food-choice task and on spontaneous behaviors. Secondly, by performing PET imaging with the [^{18}F]2FNQ1P 5-HT_6R specific marker, we investigated the 5-HT_6R's occupancy in cortical and subcortical regions that may be linked with the induced behavioral changes. Results showed that activating 5-HT_6R transmission reversibly increased food motivation parameters. However, drug effects on spontaneous behaviors were individual- and dosage-dependent. Sub-acute administration of WAY-208466 was more effective in reducing anxiety-like behaviors in the most anxious animals, whereas the chronic protocol resulted in an overall increase in activity levels, characterized by an increase in movements and object-directed behaviors, particularly with the highest dose and in the least active animals. PET imaging demonstrated that not only the striatal regions but also the limbic and cortical regions, could sustain these behavioral changes. All together, these results show that this 5-HT_6R agonist fulfills the objective of increasing food intake but only partially achieves its anxiolytic purpose. Nevertheless, we suggest that specific targeting of 5-HT_6Rs is a potential option for treating AN-R patients with SSRI-resistant symptoms.

INVESTIGATING THE BRAIN RHYTHMS SUBSERVING ATTENTION SPOTLIGHT DYNAMICS USING HIGH RESOLUTION MEG

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The brain's inherent limitations in parallel processing necessitate the implementation of attention as a fundamental mechanism to prioritize incoming information. Recent non-human primate experiments have used real-time decoding to show that attentional sampling of visual information is rhythmic involving mainly ~8-12Hz and 4-5Hz processes. These investigations are constrained by significant limitations, which encompass challenges associated with instructing animals to perform multiple tasks related to attention and achieving comprehensive coverage of the entirety of the brain. High precision magnetoencephalography (MEG) now allows to record brain activity at spatial resolutions up to the laminar level in humans.

In this study, we combined high-resolution MEG and machine learning to enhance our understanding of the rhythmic nature of attentional processes. Participants performed two versions of an attention task over three MEG sessions while maintaining central fixation. The degree of validity of the cue (100 or 90%) indicating the side to attend was manipulated in blocks. Explicit switch instructions were occasionally delivered to the subjects. Our goal was 1) to reproduce high-decoding of spatial attention obtained from intracortical signals, 2) characterize the rhythmic characteristics of this decoding within the frequency ranges of approximately 8-12Hz (alpha) and 4-5Hz (theta), and 3) characterize the influence of task instructions on both the accuracy of decoding attention and the associated rhythmic patterns. Our preliminary findings indicate that during blocks of 100% validity, it is feasible to decode spatial attention from MEG sensor-level signals with a significantly heightened accuracy exceeding chance levels in group analysis. Moreover, our investigation reveals that this accuracy is more pronounced in visual channels compared to non-visual channels. We show that this accuracy was predictive of whether short or long reaction times (RT) would be produced. Furthermore, we have demonstrated that the temporal-frequency content of the decoding accuracies exhibits an augmentation in alpha and theta oscillatory components. This content is anti-phased on trials associated with fast RT as compared to trials with slow RT, possibly indicating that response speed is predicted by the spatial localization of attention at the time of target presentation. Decoding performance was lower (though still significant) on 90% validity block. Taken together, our outcomes illustrate the viability of deciphering spatial attention on a single-trial basis using MEG signals. We anticipate that a source-level analysis will offer an improved understanding of how the attentional spotlight is regulated by the fronto-parietal attentional network.

Stronger alpha and beta power in healthy adults is related to more efficient anticipatory postural control in the bimanual load-lifting task

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Every day we perform multiple motor actions, and many of them require motor anticipation in order to perform them properly. For example, when a waiter needs to upload a glass from his tray he adjusts his posture on the tray side in order to avoid destabilizing upward rotation of the arm being unloaded. Specifically, this anticipatory postural adjustment requires inhibition of the motor command associated with the initial postural maintenance, involves bimanual coordination and requires that the same muscles in both arms are involved. Such anticipatory behavior requires a long maturation (Schmitz et al., 2002) and is strongly altered in children with autism spectrum disorder (ASD; Schmitz et al., 2003).

To determine the neural mechanisms underlying anticipatory motor behaviour, we recorded magnetoencephalography (MEG) using CTF sensor array composed of 275 axial gradiometers in 16 neurotypical adult participants who performed bimanual load-lifting task. During the task, subjects were instructed to move a load attached to their left forearm with the right arm. Elbow rotation of the left forearm was controlled as a measure of anticipatory control, so that the lower is elbow rotation amplitude the more efficient is motor anticipation. We hypothesized that more efficient motor anticipation will be associated with better inhibition in the right hemisphere, and as a result lower elbow rotation, mediated by stronger alpha/beta synchronization.

Raw data were preprocessed using MNE-python toolbox (v.1.3.0). We used the linear constraint minimal variance (LCMV) beamformer to localize the brain activity. Time-frequency analysis ([-1.7 to 1.2s] time interval, relative to the movement onset; 3-30Hz) was performed for individual trials using superlet transform (https://github.com/TransylvanianInstituteOfNeuroscience/Superlets/tree/main). As beta activity in humans is rather bursty than oscillatory, in the beta range we assessed bursts of brain activity in the 13-30Hz range (https://github.com/maciekszul/burst_detection), and then estimated their volume as a possible measure of inhibition (Enz et al., 2021). To assess the relationship between elbow rotation and brain activity in the alpha and beta frequency ranges, we estimated spearman correlation between elbow rotation and alpha power (8-12Hz) or beta bursts volume (13-30Hz) for each time bin in the time interval close to movement onset [-0.5 to 0.1s] and in each brain source. Permutation cluster test revealed a significant negative correlation for the alpha power, most pronounced in [-0.4 to -0.25s] latency range, and for the beta bursts volume in [-0.3 to -0.1s] latency range. The effect was localized in the primary motor cortex and adjuscent regions.

These preliminary data demonstrate that anticipatory postural adjustment of the left arm are related to the preceding the activity in the alpha and beta bands, so that the higher is the alpha power or the beta bursts volume, the more efficient is adjustment and the lower is elbow rotation. Further analysis of the interaction between alpha and beta activity, as well as processing of the data under control and learning

conditions, will help to better separate the roles of alpha and beta activity in brain communication underlying motor anticipation in healthy brains and in ASD.

Fast and reliable hand motor imagery decoding based on beta burst rate modulations

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Background: Since the characterization of the event-related desynchronization (ERD) and synchronization (ERS) phenomena in the mu and beta frequency bands [1], the Brain-Computer Interface (BCI) community has heavily relied on band-limited power changes as the classification feature of interest. However, recent findings in neuroscience have challenged the idea that signal power best describes the movement-related modulation of brain activity, especially in the beta frequency band. Beta band activity has been shown to occur in short, transient events termed “bursts” rather than sustained oscillations on a single-trial level [2]. In a recent study we showed that the analysis of beta bursts during hand motor imagery (MI) can be advantageous to beta power in terms of classification [3], confirming the hypothesis that on the single-trial level beta burst rate modulations are more behaviorally relevant than beta band power changes.

Approach: In this work we extend our approach by simplifying the algorithm to transform brain signals such that we gain access to measures of waveform-resolved burst rate. We propose a simple algorithm that can take advantage of an arbitrary number of recorded signals while being computationally efficient, thus constructing decoding features that are comparable to state-of-the-art in BCI. We analyze the activity during “left” and “right” hand MI from multiple open EEG datasets [4-7]. Using a new burst detection and waveform analysis algorithm [8], we select specific beta burst waveforms whose rate is expected to be maximally modulated during the task. Then, we use these waveforms as kernels and convolve the raw signals with each waveform. The resultant signals which comprise a proxy of specific burst rates corresponding to each of the kernels are fed to the common spatial patterns algorithm (CSP) [9] and its output is used in order to assess the decoding score using linear discriminant analysis (LDA) [10]. We compare these classification features that describe the modulation of burst rate for bursts with distinct waveforms with signal power based on a classic CSP approach in the beta and mu frequency bands [11] in a pseudo-online fashion. To do so we use two approaches: an incremental increase in the window used for decoding and a sliding window approach (figure 1). Also, we assess whether the number of band-passed features provided as input to the CSP algorithm can significantly affect the decoding score by using both a single filter and a filter bank approach [12] (figure 1).

Preliminary Results: The waveform-resolved burst rate is on average superior to beta band power throughout the duration of the MI tasks irrespective of the number of power features provided to the CSP algorithm and the window technique (incremental or sliding) used. It is also usually superior to band power following filtering in the mu and beta bands early in the trial period, but conversely inferior later in the trial especially when using the incremental windowing approach.

Significance: This work demonstrates that BCI applications could benefit from utilizing beta burst activity by providing reliable decoding performance often needing only a short amount of data. This analysis paves the way for a real-time adaptation of the proposed methodology.

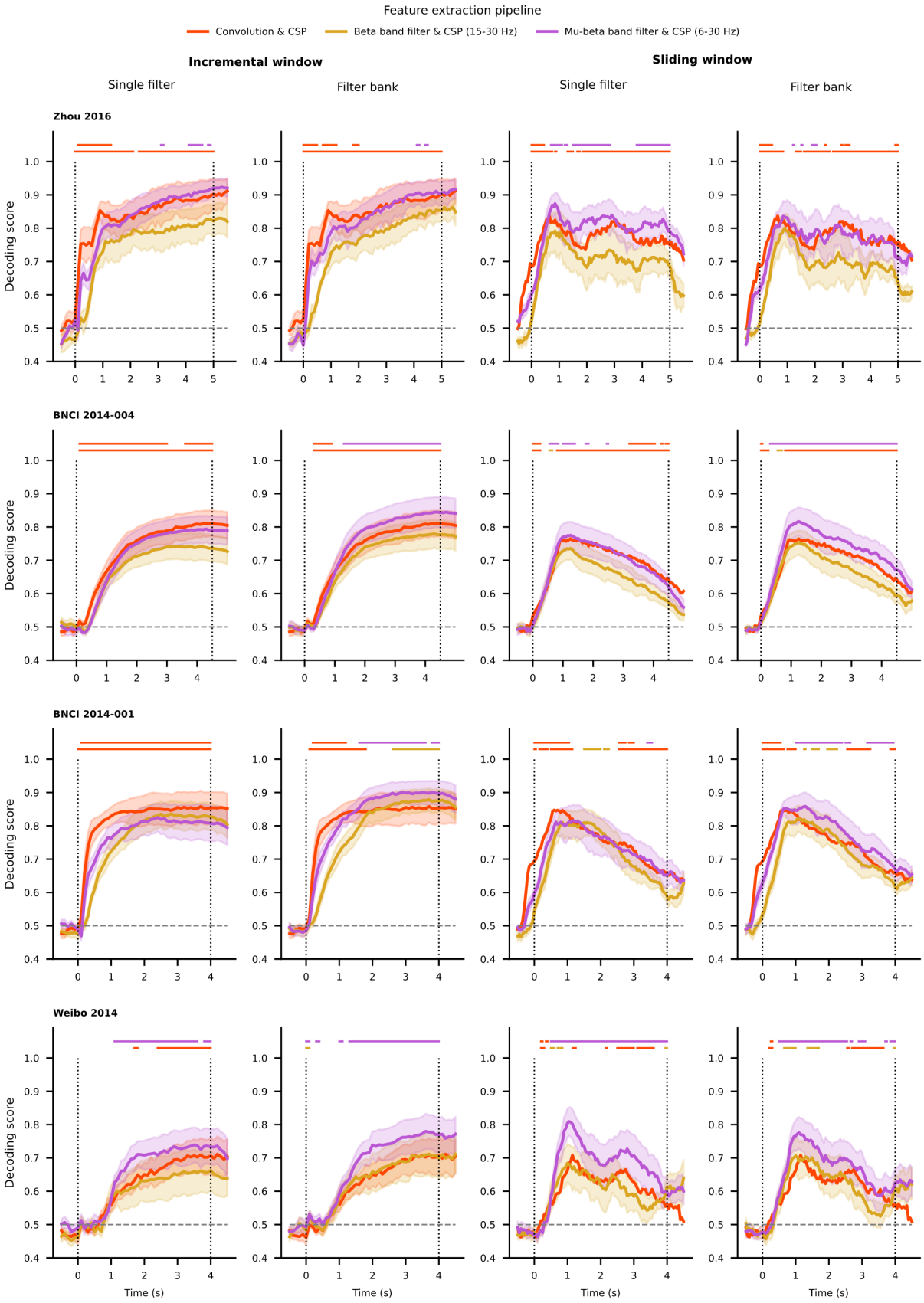

Figure 1. Time-resolved decoding results in binary “left” versus “right” hand motor imagery classification. Three techniques for creating features are assessed: the convolution of raw signals with a selection of burst waveform kernels (red), beta band (15-30 Hz) filtering (gold) and mu-beta band (purple) filtering (6-30 Hz), all of which are fed as input to the CSP algorithm before using LDA in order to estimate the classification accuracy. Each row corresponds to a different EEG dataset and depicts across-subjects average decoding accuracies. The first two columns correspond to a pseudo-online decoding paradigm based on the incremental window

approach. Using steps of 100ms duration, a classifier is trained on all available data up to each time point. The last two columns correspond to a pseudo-online decoding paradigm based on the sliding window approach. Using a window of 1s duration (centered on the middle time point) and sliding the window by 50ms each time a classifier is trained on all data of each time window. For either window approach, both a single filter or a filter bank approach are implemented and compared to results based on the convolution technique. Above each subplot, two colored lines indicate which feature extraction technique yields superior decoding results at each time point based on permutation test results between the pairs: convolution – beta band filtering and convolution – mu/beta band filtering, corrected for multiple comparisons. Dotted vertical lines indicate the beginning and end of the trial. Dashed horizontal lines indicate the expected chance level.

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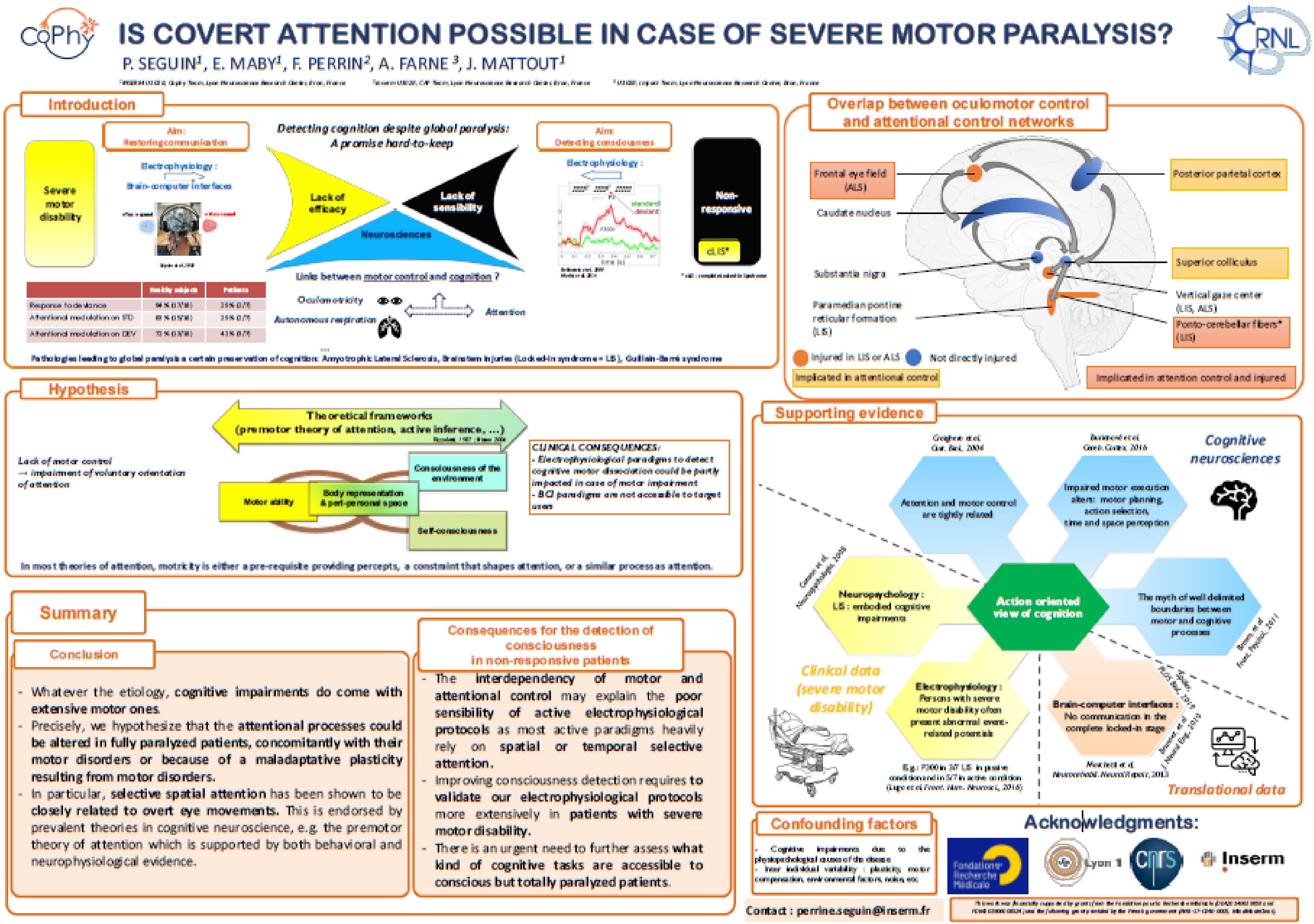
IS COVERT ATTENTION POSSIBLE IN CASE OF SEVERE MOTOR PARALYSIS?
P. SEGUIN[1], E. MABY[1], F. PERRIN[2], A. FARNE [3], J. MATTOUT[1]
Introduction
Severe motor disability
Aim: Restoring communication
Electrophysiology : Brain-computer interfaces
Detecting cognition despite global paralysis: A promise hard-to-keep
Lack of efficacy
Lack of sensibility
Neurosciences
Links between motor control and cognition ?
Oculomotricity
Autonomous respiration
Attention
Aim: Detecting consciousness
Electrophysiology :
Non-responsive
cLIS*
Healthy subjects
Patients
Response to deviance
Attentional modulation on STD
Attentional modulation on DEV
Pathologies leading to global paralysis a certain preservation of cognition: Amyotrophic Lateral Sclerosis, Brainstem injuries (Locked-in syndrome = LIS), Guillain-Barré syndrome
Overlap between oculomotor control and attentional control networks
Frontal eye field (ALS)
Caudate nucleus
Substantia nigra
Paramedian pontine reticular formation (LIS)
Posterior parietal cortex
Superior colliculus
Vertical gaze center (LIS, ALS)
Ponto-cerebellar fibers* (LIS)
Injured in LIS or ALS
Not directly injured
Implicated in attentional control
Implicated in attention control and injured
Hypothesis
Lack of motor control → impairment of voluntary orientation of attention
Theoretical frameworks (premotor theory of attention, active inference, ...)
Motor ability
Body representation & peri-personal space
Consciousness of the environment
Self-consciousness
CLINICAL CONSEQUENCES:
- Electrophysiological paradigms to detect cognitive motor dissociation could be partly impacted in case of motor impairment
- BCI paradigms are not accessible to target users
In most theories of attention, motricity is either a pre-requisite providing percepts, a constraint that shapes attention, or a similar process as attention.
Supporting evidence
Cognitive neurosciences
Attention and motor control are tightly related
Impaired motor execution alters: motor planning, action selection, time and space perception
Neuropsychology : LIS : embodied cognitive impairments
Action oriented view of cognition
The myth of well delimited boundaries between motor and cognitive processes
Clinical data (severe motor disability)
Electrophysiology : Persons with severe motor disability often present abnormal event-related potentials
Brain-computer interfaces : No communication in the complete locked-in stage
Translational data
Summary
Conclusion
- Whatever the etiology, cognitive impairments do come with extensive motor ones.
- Precisely, we hypothesize that the attentional processes could be altered in fully paralyzed patients, concomitantly with their motor disorders or because of a maladaptative plasticity resulting from motor disorders.
- In particular, selective spatial attention has been shown to be closely related to overt eye movements. This is endorsed by prevalent theories in cognitive neuroscience, e.g. the premotor theory of attention which is supported by both behavioral and neurophysiological evidence.
Consequences for the detection of consciousness in non-responsive patients
- The interdependency of motor and attentional control may explain the poor sensibility of active electrophysiological protocols as most active paradigms heavily rely on spatial or temporal selective attention.
- Improving consciousness detection requires to validate our electrophysiological protocols more extensively in patients with severe motor disability.
- There is an urgent need to further assess what kind of cognitive tasks are accessible to conscious but totally paralyzed patients.
Confounding factors
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Pierre Bonnet CRNL

Temporal predictions can be formed and impact perception when sensory timing is fully predictable: for instance, the discrimination of a target sound is enhanced if it is presented on the beat of an isochronous rhythm. However, natural sensory stimuli, like speech or music, are not entirely predictable, but still possess statistical temporal regularities. We investigated whether temporal expectations can be formed in nonfully predictable contexts, and how the temporal variability of sensory contexts affects auditory perception. Specifically, we asked how “rhythmic” an auditory stimulation needs to be in order to observe temporal predictions effects on auditory discrimination performances. In this behavioral auditory oddball experiment, participants listened to auditory sound sequences where the temporal interval between each sound was drawn from gaussian distributions with distinct standard deviations. Participants were asked to discriminate sounds with a deviant pitch in the sequences. Auditory discrimination performances, as measured with deviant sound discrimination accuracy and response times, progressively declined as the temporal variability of the sound sequence increased. Moreover, both global and local temporal statistics impacted auditory perception, suggesting that temporal statistics are promptly integrated to optimize perception. Altogether, these results suggests that temporal predictions can be set up quickly based on the temporal statistics of past sensory events and are robust to a certain amount of temporal variability. Therefore, temporal predictions can be built on sensory stimulations that are not purely periodic nor temporally deterministic.

DEVELOPMENT OF A PRECLINICAL MODEL OF REM SLEEP BEHAVIOR DISORDER (RBD), A PRODROMAL PARASOMNIA OF PARKINSON'S DISEASE, IN M83 TRANSGENIC MICE

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There is a lack of preclinical models of Parkinson's Disease (PD) that chronologically reproduce the underlying progressive brain invasion by toxic intraneuronal aggregates rich in misfolded alpha-synuclein (a-Syn). It is of particular importance to model the pre-symptomatic period during which PD insidiously settles in the brain, long before the onset of cardinal motor symptoms. REM sleep Behavior Disorder (RBD), a parasomnia with loss of muscle atonia during REM sleep is a highly recognized prodromal PD biomarker at 10 years. Since RBD and PD seem to be chronologically linked, there is an interest in investigating RBD etiology because of its predictive nature. It might reflect dysfunction/degeneration of brainstem sublaterodorsal nucleus (SLD) as its genetic inactivation in rodents is sufficient to recapitulate human RBD. We hypothesize that a synucleinopathic attack might target SLD before spreading over years in the caudo-rostral brain axis.
To test this hypothesis, we used transgenic homozygote M83 mice, a widely used PD model as expressing the human a-Syn with A53T mutation and depicting PD-like behaviors around 9-months age. M83 mice (5-months age) were prepared for polysomnographic and video recordings to assess whether they might develop age-dependent sleep alteration and RBD during prodromal period. A second sample of M83 mice received bilateral stereotaxic infusions of murine preformed a-Syn fibrils (mPFFs, van Andel Institute) into SLD to induce an additional synucleinopathy targeting REM sleep circuits. Mice were recorded every 2 weeks until occurrence of PD-like signs. Wake, Slow Wave Sleep and REM sleep were classified and quantified based on EEG/EMG signals.
Our ongoing experiments indicate that control M83 mice started to experience RBD-like events at 9/10months age, characterized by sudden, rapid and jerky movements during REM sleep, easily distinguishable from those during Wake. A constant decrease with aging was noticed in daily PS amounts (from 91.0+/-2.8min to 64.8+/-1.3min at 5- and 9-months age). Of great interest, mPFFs-treated M83 mice also experienced intense RBD during REM sleep with a concomitant state fragmentation resulting from increased bout numbers of shorter duration, only 1-5 weeks after the recording start, likely with accelerated physio-pathological kinetics compared to that in control mice. As reported in patients, RBD may suppress REM sleep in M83 mice, especially when endowed with alteration of REM sleep circuits.

LINKING PLACE WITH VIEW: ORGANIZING SPACE THROUGH SACCADES AND FIXATIONS BETWEEN PRIMATE POSTERIOR PARIETAL CORTEX AND HIPPOCAMPUS

Human primarily use vision to explore and guide actions in space. It is known that posterior parietal cortex (PPC) provides a map of visual space to guide saccades to salient cues, while the hippocampus provides a memory-based cognitive map of the environment. How does the visual map interface with the cognitive map during navigation? To probe the link between view and place, we compared neural activity in the intraparietal sulcus, and hippocampus of macaques navigating in a virtual maze. When analyzed as a function of animal's position in the virtual environment, more neurons displayed spatial selectivity in the PPC than in the hippocampus. We hypothesize that PPC would support self-position, along with the hippocampus, via the processing of environmental visual cues through explorative saccades and fixations. Indeed, neural selectivity to "place" in both regions appeared to result from saccades and fixations directed to salient landmarks and routes during virtual navigation. First, we observed a population of parietal cells whose saccade-related responses differed according to monkeys' position into the maze. However, we showed that position-selectivity did not solely correlate with simple oculomotor dynamics. Instead, it would rather be driven by sensori-motor contexts of the task. Second, parietal cells and, to a lesser extent, hippocampal ones, were driven by viewing behavior, and divided into two populations that preferentially responded to direct fixation of landmarks, or of maze paths (i.e. landmarks in the periphery of the visual field). The parietal landmarks cells displayed a higher activity when the monkey's eyes directly fixated a landmark, while the hippocampus ones were less impacted by the precise position of the visual cue on the fovea. Thirdly, we demonstrated that spatial selectivities arose from this recruitment of the cells encoding specific visual cues, providing a task-relevant segmentation of the maze. Finally, a great part of PPC and hippocampus cells responded to the appearance of the landmarks on screen, and some even expressed selectivity to features such as their side of appearance or identity. At the population level, both regions showed an anticipation of the landmarks appearance, suggesting the existence of a cognitive map of the spatial layout, and an active part in memory-directed visual exploration. Overall, our results support a dynamic flow of activity between the parietal cortex and the hippocampus, organised along directed saccades and fixations towards anticipated landmarks, at strategic positions, leading to a contextual, task-based processing that ultimately links action and objects in space and memory.

Toan Nong

It remains controversial whether the ability to represent the world from the perspective of another (mentalising), is confined to humans[1–3]. Here we characterised the computational mechanisms used by Guinea baboons (*Papio papio*) living in a social colony. They freely came to play a strategic coordination game with any other baboon (social condition), and the same game alone (solo condition). In both conditions, they were interacting with an identical artificial agent. We combined computational models of coordination with an experimental setup allowing baboons to interactively play together via touchscreen devices inside their enclosure. Notably, this approach required baboons to interact with conspecific fellows, requesting no direct human intervention or teaching. Performance was better in the social than in the solo condition. In the social condition, a computational mentalising model that predicts the effect of one's actions on the partners' outcome[4,5] accounted for baboon's behaviour much better than reinforcement learning[6,7], Bayesian[8–11] or heuristic models[12] that lacked mentalising components. Such computations accounted best for behaviour in the social condition only, because when they played alone, the same baboons used a win stay/lose switch strategy. Together, these findings indicate that computations required for mentalising are evolutionary advantageous and are present in the Guinea baboon.

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Title: COOPERATIVE AND ADVERSARIAL WORLDS IN ACTIVE INFERENCE

Authors: M. Joffily (CNRS, Lyon, France) and T. van de Laar (Eindhoven University of Technology, Eindhoven, Netherlands)

Abstract: We investigate the consequences of prior beliefs about cooperative and adversarial worlds in decision making within the framework of active inference. Active inference extends the free energy principle with action selection through expected free energy minimization, and offers a principled probabilistic account of how surprise minimization can be achieved in partially observable environments. We perform numerical simulations inspired by the 2-urn Ellsberg's paradox, a classic paradigm in behavioral economics used to assess people's preferences over risky (known probabilities) and ambiguous (unknown probabilities) prospects. We show that ambiguity- and risk-seeking behavior can be explained as a consequence of Bayesian prior beliefs about a cooperative or adversarial world in the 2-urn task. Our results support the probabilistic modeling view on choice behavior regarding risky and ambiguous opportunities, which has direct implications for understanding learning, cognitive biases, and decision making in humans and other animals.

*** 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.

Neuro-Day Abstract (08/02/2024)

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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Abstract (487 words)

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 python 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 the 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 neuronal 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 $[^{15}O]H_2O$ injections recorded simultaneously 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 bicuculline 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 such 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 effectiveness 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.

Distinct roles played by dopamine and serotonin systems in approach-avoidance behavior: a pharmacological study associated with PET imaging in non-human primate.

Lisa Gauthier[1, 2], Guillaume Drui[1], Justine Debatisse[1, 3] Yosuke Saga[1], Mathilde Millot[1], Eva Martinez[1], Elise Météreau[1], Karine Portier[2,5], Philip N Tobler[6], Léon Tremblay[1, 2] and Benjamin Pasquereau[1, 2]

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ABSTRACT

Approaching pleasant, positive stimuli and avoiding unpleasant, negative ones is a core element of adaptive behavior in response to important, emotionally valenced stimuli. Biased approach-avoidance behaviors are a hallmark of many psychiatric disorders such as anxiety and impulsive disorders. To regulate appetitive and aversive motivational states involved in these types of behaviors, the positive or negative valence is thought to be regulated by the dopamine (DA) and serotonin (5-HT) systems. However, the specific roles played by DA and 5-HT in approach-avoidance tendencies remain unclear. Some studies suggest distinct involvement, while others describe a combined regulation of approach-avoidance behaviors by both DA and 5-HT systems. To address this issue, we compared the effects of DA or 5-HT manipulation in 4 macaques trained to perform an approach-avoidance task in which they had to adapt their behavior depending on the valence of visual stimuli. We increased synaptic dopamine levels by injections of methylphenidate (MPH) (0.1 mg/kg), while 5-HT levels were selectively boosted by injections of fluoxetine (FLX) (4 mg/kg). In addition, we conducted PET scans with [^{11}C]PE2I or [^{11}C]DASB to identify where in the brain these two reuptake inhibitors acted to modulate DA/5-HT systems and further affect monkeys' choice. Consistent with a selective role of DA in regulating approach responses, monkeys exposed to MPH showed an increase in the willingness to work to get rewards and few effects on aversive condition. Combined with PET imaging, our results suggest a specific role of DA in the processing of positive information within the anterior striatum. Monkeys exposed to FLX showed a better self-control and task engagement in aversive condition, when animals had to avoid the air-puffs. These drug-induced effects indicate a stronger involvement of 5-HT system in regulating the processing of negative information required to drive avoidance behavior. In PET results, the neural network supporting this negative valence system appears to be larger distributed between the limbic cortical regions and the anterior striatum. Hence, in addition to a key role in appetitive processing modulated by the DA system, our results shed light on the involvement of the anterior striatum in aversive processing modulated by the 5-HT system. Together, DA and 5-HT systems appear to play complementary roles in the control of motivational states involved in approach-avoidance behaviors.

THE SEROTONIN LESION INDUCED BY MDMA (ECSTASY) IN NON-HUMAN PRIMATE PRODUCES AN ACUTE ANXIETY DISORDER AND A DISTURBANCE OF FLUOXETINE THERAPEUTIC EFFECTS

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3,4-methylenedioxymethamphetamine (MDMA, "Ecstasy"), a recreational drug, is a potent serotonin (5-HT) releaser which acts like selective serotonin reuptake inhibitors (SSRI), drugs widely used in psychiatric disorders. MDMA has been proposed as treatment for some psychiatric disorders, like post-traumatic stress disorder, autism, and anxiety-related disorders, where SSRI resistance can exceed 60% of patients. However, in non-human primates (NHP), MDMA can cause irreversible lesions in 5-HT terminal fibres, where therapeutic effects of SSRIs (ex: fluoxetine), can be exerted. This emphasises the risk of using MDMA therapeutically without a preclinical safety study to determine its effects. This study conducted on NHP had two aims: 1) To determine the severity of MDMA-induced serotonergic lesion and its effects on behaviour and 2) To study interactions between a prior possible protective fluoxetine treatment and the impact of MDMA lesion on post-MDMA fluoxetine treatments. After receiving MDMA, all monkeys (n=7) exhibited increased anxious-like behaviours for two weeks, before returning to pre-MDMA rates for most animals. This acute anxiety-related effect was characterized in the aversive context of an approach-avoidance behavioural task, where monkeys had significantly lower completion rates and higher escape rates. Three weeks after MDMA administration, [^{11}C]DASB-PET imaging specific to the 5-HT transporter (SERT) revealed reductions in SERT density, confirming previous findings on MDMA-induced toxicity in 5-HT axon terminals. The ventral striatum, anterior caudate and insula were most affected while the pallidum and raphe nucleus preserved their SERT density, with increases in some animals. Before MDMA administration, fluoxetine treatments induced beneficial effects on behavioural markers of anxiety by increasing completion rates and lowering escape rates in aversive context in 5/6 monkeys. After MDMA administration, beneficial effects of fluoxetine were lost in 5/6 animals. These findings show that the severity of anxious-like behaviours and the efficacy of fluoxetine in NHP depends on the integrity of 5-HT projections. In conclusion, the administration of MDMA as a therapeutic strategy in SSRI-resistant psychiatric disorders appears risky and should be used with caution, based on these NHP results showing major adverse effects of MDMA via production of an acute anxiety disorder, and loss of fluoxetine therapeutic effects in most of our animals.

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.

Abstract CORTEX MAG – poster NEURODAY

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Cross-species evolution of brain energy architecture measured by PET FDG in mammals

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Introduction:

Glucose is the primary energy of in the brain of mammalian species. In humans, 20% of the oxygen and therefore calories, are consumed by the brain (Plattner and Bibb 2012). In addition, cerebral organization and function are closely related to metabolic activity (Passow, Specht et al. 2015) and energy metabolism is one of the key tradeoffs of mammalian evolution (Aiello and Wheeler 1995). However, and quite interestingly, variations in mental and motor activity does not significantly change the overall brain's metabolism (Sokoloff, Mangold et al. 1955). Thus, cerebral metabolism at rest is a fascinating candidate to explore the evolution of brain function. **Human brain function is characterized by its extremely high cerebral metabolic cost** when compared to other species. This may be imposed by its large number of neurons (Herculano-Houzel 2012). Our cerebral energy consumption was found to be so elevated relative to other species, that the sustainability of our brain function may have been only possible thanks to the discovery of fire, and the cooking of food, thus enhancing digestion efficiency (Herculano-Houzel 2012).

Cerebral glucose consumption can be imaged using fluorodeoxyglucose (FDG) radiotracers and positron emission tomography (PET). This technique enables to digitally map glucose metabolism variations in the whole brain of different species. In the following, we gathered PET FDG datasets of 11 species (mice, rats, pigs, dogs, cats, mouse lemurs, marmosets, vervets, macaques, chimpanzee, humans) shared by 10 laboratories across 6 countries. These data correspond to the healthy control cases of previously publish PET neuropathology studies (Kim, Lee et al. 2010, Deleye, Verhaeghe et al. 2014, Barks, Parr et al. 2015, Laaksonen, Kallioinen et al. 2018, Latimer, Shively et al. 2019, Malbert, Horowitz et al. 2019, Xu, Peremans et al. 2022). We use this cross-species international dataset to specifically address the unexplored question of the evolution of cerebral glucose metabolism across mammalian species.

Aim:

We aim to ***characterize the mammalian blueprint of the brain metabolism and to characterize key evolutionary divergence (or conservation) related to the cerebral glucose metabolism.*** This study is expected to contextualize the human brain metabolism, with respect to other primate/mammalian species and give us insight into its evolution. In particular, *it will shed critical light on whether specific human brain regions consume a high level of energy when compared to other species, accounting for human specific cognitive abilities beyond anatomical and computational specificities.* In addition to this main aim, we aim to ***create a database to share mammalian PET FDG images and templates*** (Fig. 1, A).

Method:

Data

Species	PET	Anesthesia	N
Felis catus	(Kim, Lee et al. 2010)	ketamine	8
Microcebus murinus	NP	isoflurane	7
Canis lupus	(Xu, Peremans et al. 2022)	isoflurane	12
Macaca mulatta	NP	isoflurane	7
Homo sapiens	(Laaksonen, Kallioinen et al. 2018)	sevo/iso/keta/propo/dex	160

Callithrix jacchus	NP	isoflurane	4
Rattus norvegicus	(Deleye, Verhaeghe et al. 2014)	isoflurane	58
Sus scrofa	(Malbert, Horowitz et al. 2019)	isoflurane	18
Pan troglodytes	(Barks, Parr et al. 2015)	propofol	4
Mus musculus	(Deleye, Verhaeghe et al. 2014)	isoflurane	25
Chlorocebus aethiops	(Latimer, Shively et al. 2019)	isoflurane	20

Table 1: Description of available data for each species in each modality and data origin. Abbreviations: sevoflurane (sevo); isoflurane (iso); ketamine (keta); propofol (propo); dexmedetomidine (dex), not published yet (NP).

PET FDG pre-processing with easyMMRIbrain: Working with PET FDG images of different species requires strong adaptation of any pipeline to the image quality, contrast, etc. Our preprocessing pipeline "***EasyMMRIbrain***" -for Easy Mammalian MRI Brain- is able to build a PET FDG template for each species. This PET FDG template enables an optimal co-registration of the individual PET FDG images into a common space for cross-species analyses. It also facilitates one of the most challenging steps which is the co-registration of a T1 or T2 anatomical reference template to a PET FDG template, thus allowing co-registration with the atlas. This aspect of the pipeline allows cross-species co-registration, study-based template generation, high-resolution segmentation, fluid transformation from the reference template or atlas to the study template, to the individual subject space and back, as well as efficient 3D surface reconstruction. It also generates automated quality check indicators of PET images from different species. This process also allows to display the PET FDG signal on a 3D surface with Freesurfer (Fischl 2012), any statistical comparisons in a common space, as well as atlases-based or individual-based signal extraction. *EasyMMRIbrain* achieves optimal processing of both lissencephalic and gyrencephalic brains.

PIDM to identify whole brain mosaic evolution across the different species: This technique, developed in our recent article (Garin, Garin et al. 2022), employs matrices to highlight the areas where each species of interest consistently and significantly deviates from predicted ranges. PIDMs recapitulate all possible PGLS analyses based on every conceivable combination of areas within a species, coping with multiple comparisons.

Preliminary results:

Preliminary results indicates a primate "over-metabolic" activity in the somatosensory cortex as compared to cats, mice, rats and pigs. Indeed, this region emerges as one of the three statistically most active cortical region in chimpanzees, macaques and marmosets as compared to other species (Fig. 1, A, B, C).

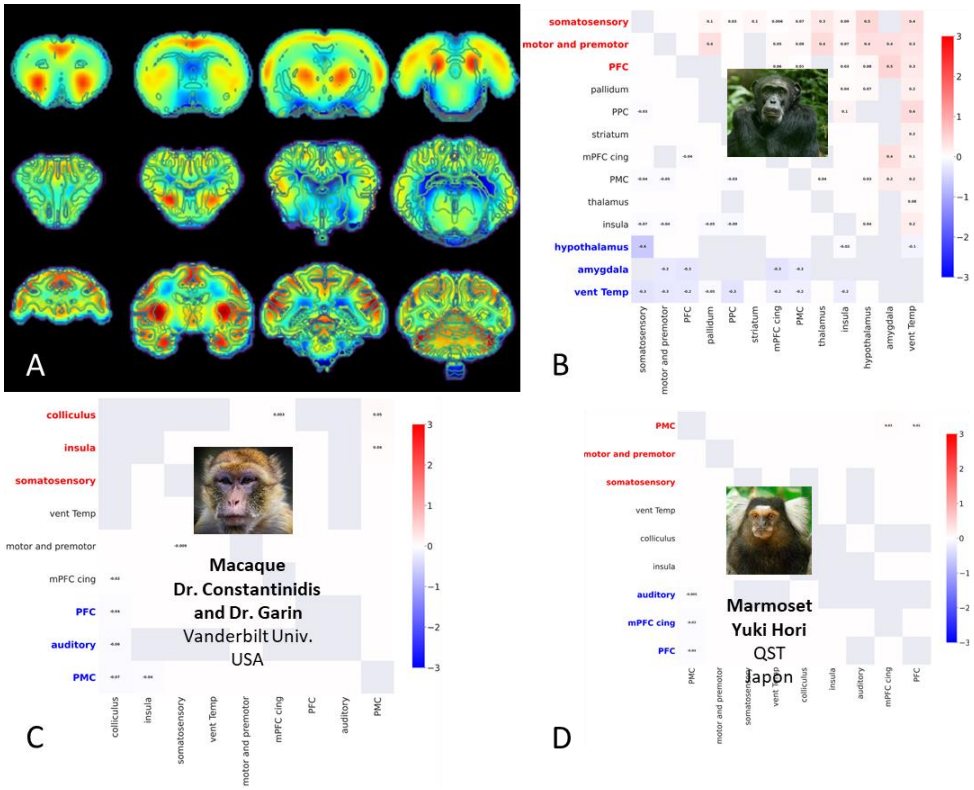

Figure 1 | PET FDG templates for 3 different species: rat (top), dog (middle), macaque (bottom)(A). The templates were created using EasyMMRIbrain. PET FDG prediction interval matrices in chimpanzee (B), macaque (C), marmoset (D), as computed using PIDM. Somatosensory cortex is overactive in all three primate species relative to the other species.

Conclusion:

In summary, by providing new biomarkers of cerebral evolution, this study is expected to contribute to theories on “where” and “how” human intelligence has evolved.

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Title: The role of the lexicon and inductive biases in the representation of abstract relational concepts.

Authors: Emilie Serraille & Jean-Rémy Hochmann
Presenting author: Emilie Serraille
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Analogical reasoning is the capacity to reason about abstract relations. The Relational Match-to-Sample task (RMTS) was designed to test this ability (Premack, 1983), asking participants to match pairs of stimuli that exemplify the same relation; e.g., *AA* should be matched to *BB* as both exemplify the relation same; *AB* should be matched to *DE*, as both exemplify the relation different. Non-human animals and children younger than 5 typically fail this task (Hochmann et al., 2017). However, they succeed in other abstract matching tasks (e.g. number matching task) and in other relational tasks such as the same/different discrimination task, where they need to respond differently to same and different pairs, suggesting they do possess some representation of the abstract relations same and different.

Two accounts have been offered for these results. First, the infant/animal representations of same and different may not afford success in RMTS, and novel representations must be acquired around the age of 4 to enable analogical reasoning (Hochmann, 2022). Second, young children may fail at RMTS, not because they lack the proper representations, but because they exhibit an object bias that prevents them from considering relational hypotheses when trying to solve the RMTS (Kroupin & Carey, 2022). The second hypothesis predicts that modifying the inductive bias in favour of relational hypotheses should improve performance in RMTS, even in younger children. The representational hypothesis, in contrast, predicts that modifications of inductive biases should only be effective after the representational change.

In Experiment 1, we first replicated previous findings showing that 3 and 4-year-olds fail at RMTS, while 5- and 6-year-olds succeed (N=24 per age group). In Experiment 2, 3-, 4-, 5- and 6-year-olds (N=24 per age group) were tested on the RMTS after taking a same/different discrimination task aimed at priming the representations of the relations same and different. Results showed that all age groups succeeded at the discrimination task. Four- to six-year-olds succeeded at the RMTS, while 3-year-olds still failed (Figure 1). Moreover, in both experiments, we observed a strong association between knowing the words “same” and “different” (as testified by children’s spontaneous or elicited production of the words at the end of the experimental session), and success in RMTS.

Finally, doubling the sample size of the 4-year-olds tested in Experiment 2, we analysed children who produced the words “same” and “different” (N=25) and those who do not (N=23), separately. Again, both groups succeeded on the discrimination tasks, but only the group that produced the words succeeded at the RMTS. Moreover, in the latter group only, we observed a positive correlation between performance in the discrimination task and performance in the RMTS (Figure 2).

Overall, results suggest that a modification of inductive biases in favour of relational hypotheses is only effective in children that possess the words “same” and “different”. Thus, differences in inductive biases alone do not account for the development of analogical reasoning. Rather, a representational change signalled (and possibly caused) by the acquisition of the words “same” and “different” appears necessary.

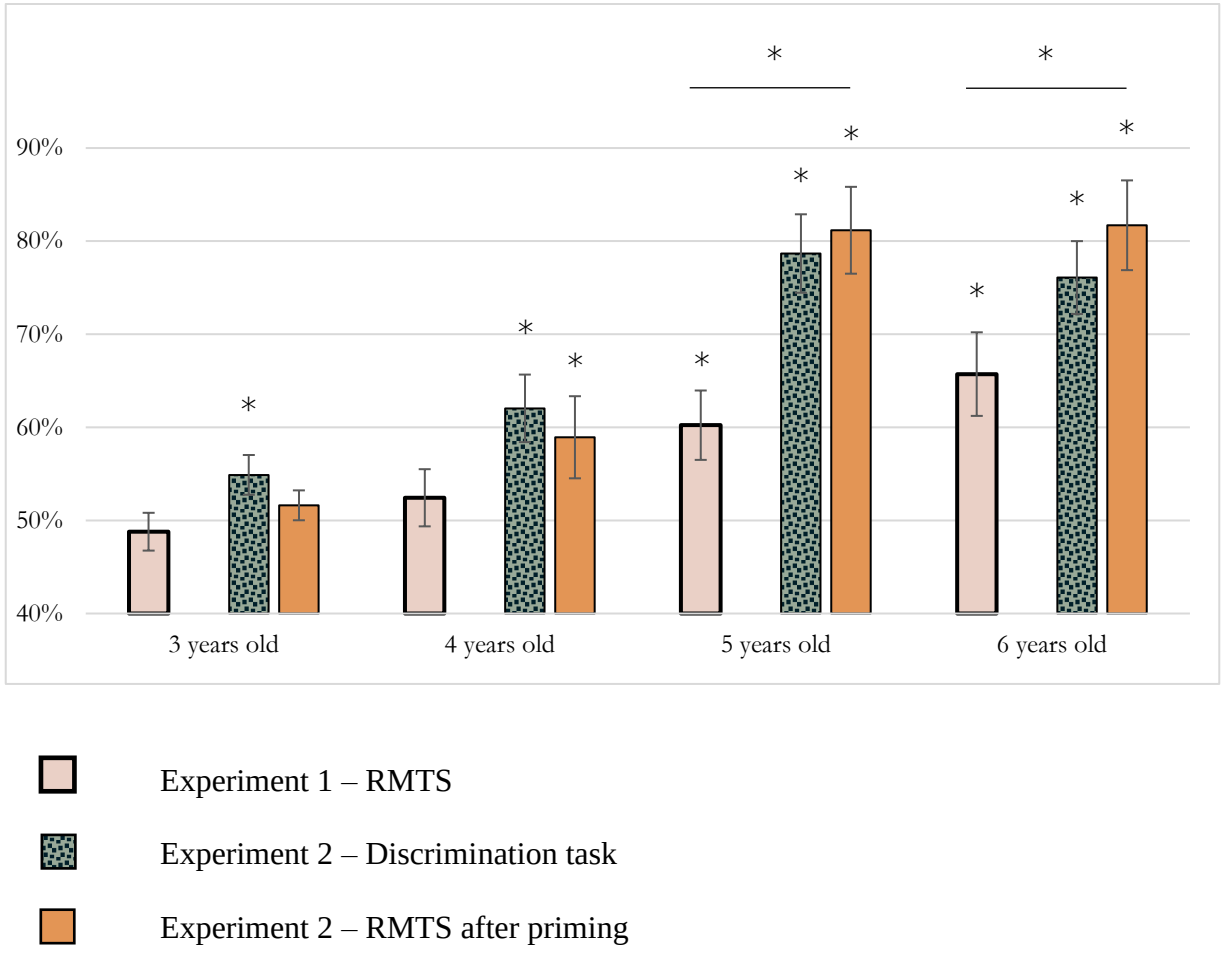
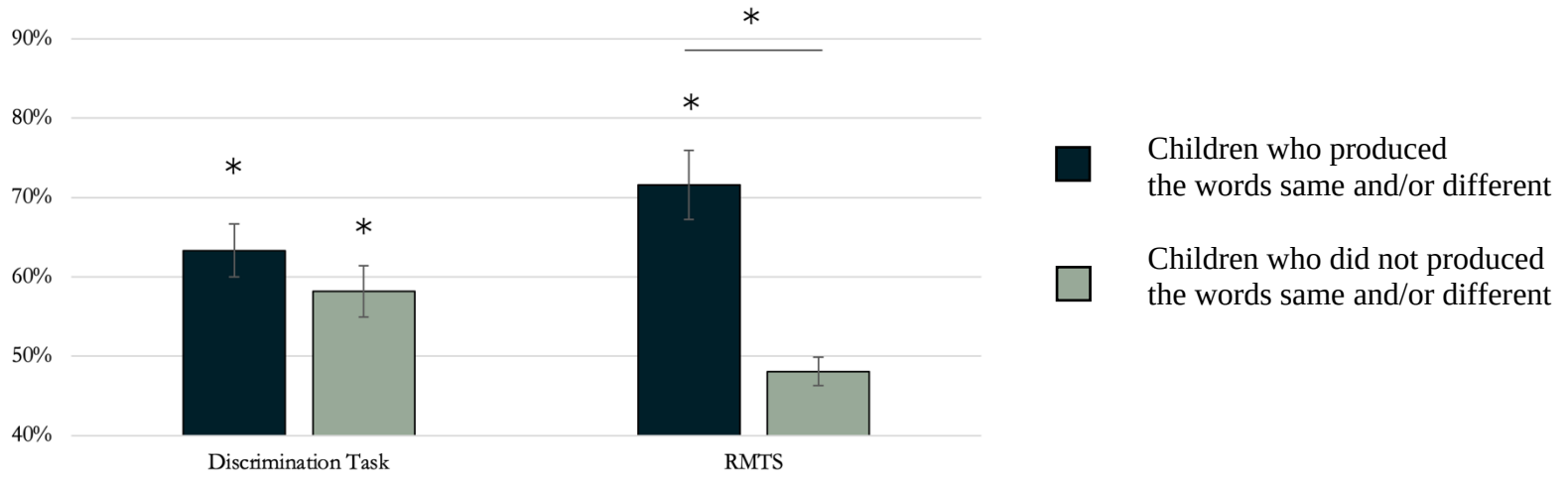


Figure 1: Mean performances for the discrimination task and the RMTS, per age-group. In Experiment 1, children were tested on the RMTS, in Experiment 2, children were tested first on the discrimination task, then on the RMTS. Chance level is considered at 50%. Error bars indicate standard errors from the mean, * indicates performances significantly higher than chance level, $p < 0.05$.

A)



B)

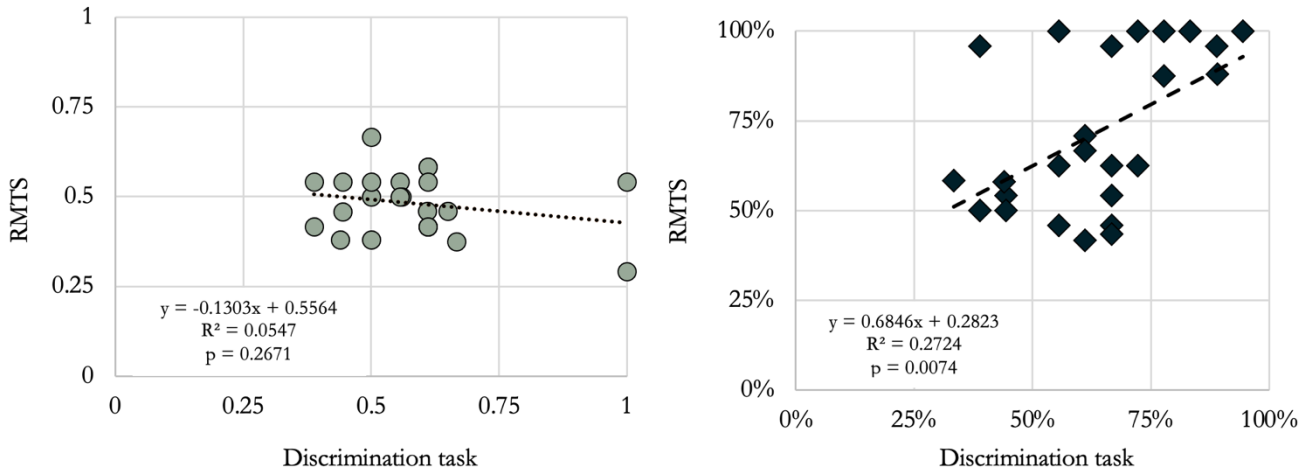


Figure 2: A) Mean performances for each task, for four-year-olds based on the production of the words same/different. Chance level is considered at 50%. Error bars indicate standard errors from the mean, * indicates performances significantly higher than chance level, $p < 0.05$. B) Correlations between performances on discrimination task and RMTS in Experiment 2 for four-year-old children based on the production of word "same" and "different".

Title: Frequency-tagging the animate-inanimate visual object categorization in human adults and infants

Authors: Céline Spriet, Emilie Serraille, Liuba Papeo & Jean-Rémy Hochmann

Human adults are very efficient at visually categorizing objects in their environment, especially animate and inanimate objects. We aim at detecting a direct, robust and automatic signature of such an Animacy visual categorization in the adult human brain, studying its symmetry and the features needed.
For this, we used a frequency tagging paradigm, coupled with electroencephalography. We recorded the scalp activity of 24 human adults while viewing images of animate and inanimate objects at a rapid frequency of 6 Hz. The animate categorization was studied by showing a flow of inanimate objects to subjects, with an oddball target (animate stimuli) every 5 images. This leads to an oddball stimulation frequency of 1.2Hz. Thus, the categorization of animate within inanimate (or vice versa) was detected by a high signal-to-noise ratio response at this oddball frequency and harmonics. We also explored the role of texture and global form of the stimuli in this categorization, by showing to subjects the texform versions of the images. Those special stimuli keep information about texture and global form but with no recognition of the stimuli.
We found evidence of an animate and an inanimate categorization with both recognizable and texform version of the stimuli, with a significant difference between recognizable and texform stimuli as well as between the animate and the inanimate condition in the recognizable version.
Thus, we can capture an Animacy visual categorization in the human adults' brain that is not fully explained by mid-level features such as the texture and the form.

Jean-Rémy Hochman

Cognitive development in preterm infants.

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.

Guillaume Marcy

Abstract:

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.

Beyond frequency bands: circuit mechanisms for bursting gamma oscillations

Di Volo Matteo, V. Douchamps, A. Torcini, D. Battaglia, R. Goutagny

Coherent oscillations of neuronal activity are ubiquitous across brain spatial and temporal scales and are detectable with Local Field Potential (LFP). Different mechanisms have been evoked in the past to explain their origin, often involving synchronous firing activity of neurons with periodic and large amplitudes oscillations at the population scale. In LFP recordings in CA1 region of mices during spatial navigation we show that gamma oscillations (30-120 Hz) are hard to reconcile with these classical models. Oscillations are indeed far from being periodic limit cycles as in the classical view of dynamical system theory. We instead observe a large diversity of oscillatory events ('gamma bursts') characterized by heterogeneous frequency and powers. The observed diversity of gamma elements puts out a challenge to structure-driven views in which oscillations with different frequencies would be generated by distinct source populations.
In order to explain the mechanisms at the origin of such oscillatory complexity we designed a computational model of balanced excitatory and inhibitory spiking. The balance between excitation and inhibition elicits a new type of oscillations, characterized by a broad range of frequencies and by irregular and low frequency spiking activity of neurons. Theoretical and numerical investigations show that large amplitudes oscillations with synchronous firing appear for strongly connected networks. Nevertheless, gamma diversity robustly emerges for most parameter combinations provided the network remains not too far, but still below a transition to strongly synchronized oscillatory firing (i.e. at the "fringe of synchrony", rather than in a regime with fully-developed synchrony). In sum, a local balanced E/I circuit at the fringe-of-synchrony is not expected to generate a gamma rhythm with a narrowly tuned frequency but, on the contrary, a diverse ensemble of transient gamma events with dynamically adjustable average frequency.

Optimal theta-gamma coupling for bursting oscillations

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Coherent oscillations of neural activity are ubiquitous across brain spatial and temporal scales and have been associated with the formation of sensory or behavioral representations [1]. Refined experimental techniques report today a new complexity of this oscillatory activity, especially in the gamma (30-100 Hz) band. Indeed, the frequency of these oscillations shows a large variability through time [2], questioning the classical view of γ oscillations being separated into different frequency bands. Oscillations appear instead in bursts characterised by rapid, synchronous neuronal firing. This is difficult to reconcile with often employed massive trial averages or with predictions from simplified computational models. In this work, I will present a new mechanisms for the emergence of bursting gamma oscillations, based on chaotic attractors in spiking networks of excitatory and inhibitory neurons. We also employ a neural mass model to reduce the dimensionality of the network, allowing us to discover a rich repertoire of dynamical phases, from bistable regimes to classical PING periodic oscillations to gamma bursts. We then study the Phase Amplitude Coupling (PAC) of gamma oscillations with a theta forcing across the phase space of the model. We show that PAC is maximum at the edge of this new bursting gamma region. This demonstrates that chaotic oscillatory bursts are capable of boosting information transfer between different neural rhythms. Altogether, we present a theoretical framework to explore the mechanisms of theta-gamma PAC and their relation with the activation of neuronal ensembles.

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Frontal oscillatory beta bursts have rhythmically distinct regimes with differing functional relevance.

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The importance of studying the transient burst-like nature of beta- and gamma-band oscillations has become increasingly clear. This approach challenges accepted interpretations of oscillatory behaviour and emphasizes the importance of examining phenomena at appropriate temporal scales, as opposed to trial averages. Diversity in the detailed temporal form of these real-time phenomena has been under-considered, yet it should provide important information about function. Here we studied such bursts at beta frequencies, and explicitly distinguished transient bursts characterized by high power (BoP) and those marked by consistent cycles (BoC) using methods tailored to capture each characteristic. Analysis of neural recordings from mice and macaques revealed two distinct and largely independent beta burst categories within the same temporal content. BoP bursts were true transients featuring a substantial amplitude peak and minimal rhythmicity, while BoC bursts were much more rhythmic, seemingly meeting a more classic definition of an oscillation. Importantly, these two classes of beta burst showed differing functional relevance within the same signal. In a search-repeat task, BoC bursts occurred more often in the search phase, whereas BoP bursts dominated the repeat phase. As such, beta frequency neural signals encompass at least two transient phenomena, each with potentially distinct functional roles.

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Foraging behaviour in a naturalistic search task in macaque monkey:

Behavioural description and LC/NA-MCC network modulation with pathway-specific chemogenetics

Foraging is central to primate life. This adaptive activity entails exploration for specific information or reward, and integration of such information over long timescales. Monitoring for behavioural consequences is key to express flexible foraging behaviour allowing for alternatively choosing to exploit known resources, for exploring other options when resources are reduced, and for stopping when resources have been depleted. The role of the Locus Coeruleus/NA system has long been thought of as an enhancement of cognitive processes. The adaptive gain theory poses that LC activity modulates signal to noise ratio in medial frontal cortex activity, and therefore impacts on behavioural flexibility (Aston-Jones and Cohen 2005).

We tested whether foraging behaviour is influenced by the locus coeruleus (LC)/noradrenergic (NA) drive on the midcingulate cortex in macaque monkeys. Monkey were tested in two versions of a spatial foraging/ search task realized in the homecage. We used pathway specific chemogenetics to target and modulate noradrenergic system afferences to the anterior midcingulate cortex (aMCC) with a vector containing a selective noradrenergic promotor and an activator receptor (CAV2 PRS hM3Dq).

Here we present the observed effect of activating DREADDs with DCZ in 2 animals, showing altered exploration especially in the more complex version of the foraging task.

Tjerk Gutteling - CERMEP

MagnetoEncephaloGraphy (MEG) provides a measure of electrical activity in the brain at a millisecond time scale. Conventional MEG systems (SQUID-MEG) use very low temperatures to achieve the necessary sensitivity. This leads to severe experimental and economical limitations. A new generation of MEG sensors is emerging: the optically pumped magnetometers (OPM). In OPM, an atomic gas enclosed in a glass cell is traversed by a laser beam whose modulation depends on the local magnetic field. MAG4Health is developing OPMs using Helium gas (^{4}He-OPM). They operate at room temperature with a large dynamic range and a large frequency bandwidth and output natively a 3D vectorial measure of the magnetic field. An earlier study using only a few sensors has provided encouraging results, showing very similar results compared to SQUID-MEG. Currently we are testing the deployment of a newly developed whole-head ^{4}He-OPM system with 48 triaxial sensors. The increase in sensors provides better coverage, more advanced noise reduction and the ability to apply source estimation. Current paradigms for testing include visual, motor- and auditory tasks.

Titre

NARCAPA: benefits of an interventional program on physical activity for children with type 1 narcolepsy

Auteurs

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Abstract

Narcolepsy type 1 (NT1) causes symptoms such as excessive daytime sleepiness and cataplexy. Comorbidities are common, including obesity, depression and attention disorders. Drug treatments are often only partially effective, motivating the use of non-pharmacological treatments including physical activity (PA).

The objectives of the study were (i) to evaluate the level of PA of children and adolescents with NT1, (ii) to relate the level of PA, measured subjectively and objectively, with the severity of symptoms and comorbidities. of narcolepsy in children and (iii) to evaluate the benefit of the intervention of a teacher in Adapted PA (APA) in these patients.

27 NT1 patients (median age 14.7 years) were included in this retrospective study following their care by an APA teacher as part of the E-HOP project, aimed at promoting APA at the Women-Mother Hospital -Child of Bron. NT1 symptoms and comorbidities were assessed before and after a 4-week APA intervention. The PA level was measured by continuous actimetry. The initial level was compared to normative data and WHO recommendations, and the links between PA and clinical data were studied before and after the APA intervention.

Before the intervention, 52.4% of the sample already had a PA level consistent with WHO recommendations. The quality of life score was higher in patients practicing extra-curricular PA. The APA intervention was associated with an increase in PA in 45% of patients. Before the intervention, the group receptive to APA tended to be less active than the non-receptive group and presented more depressive symptoms. The intervention did not generate any significant clinical change.

Despite drowsiness, young NT1 patients are generally active. The practice of extra-curricular PA is associated with a better quality of life. The APA intervention encouraged patients who were not initially very active and/or had depressive symptoms to do PA. By extending the intervention, we could hope for an improvement in the clinical picture.

Project funded by the French Society for Research and Sleep Medicine.

Pauline Mouches CRNL

Time CNN and Graph Convolution Network for Epileptic spike detection in MEG data

Magnetoencephalography (MEG) recordings of epilepsy patients present, outside seizures, epileptic spikes. Detecting those spikes allows accurate localization of brain regions triggering seizures. Spike detection is often performed manually by clinical experts. However, it is a burdensome and error prone task due to the complexity of MEG data. To address this problem, we propose a 1D convolutional neural network (Time CNN) coupled with a graph convolutional network (GCN) to classify short time frames of raw MEG recording. Compared to other recent approaches, our Time CNN model has fewer parameters to train and we propose to use a GCN to account for MEG sensors spatial relationships. Best model performances on a balanced dataset are obtained with the Time CNN-GCN with a classification accuracy of 77.5%. On a realistic imbalanced dataset, the Time CNN alone performs best (f1-score: 25.7%), while substantially outperforming state-of-the-art methods (best f1-score: 17.7%).

Behavioral study of food avoidance in anorexia nervosa patients: a gaze control study associated with food evaluation and preference tasks

Amale Zemmahi, Ludwig Ségalen, Justine Debatisse, Justine David, Elise Météreau, Amira Hammour, Natacha Germain, Catherine Massoubre, Marie-Claire Villeval, Bogdan Galusca and Léon Tremblay

Abstract (279 words)

Anorexia Nervosa (AN) is a psychiatric disorder with an often severe prognosis, characterized by irrational fear of weight gain, a strong desire to lose weight and dysmorphophobia. In order to lose weight, patients avoid high-calorie and high-fat foods. They routinely make poor choices despite knowledge of negative consequences that can lead to their death. This pathology often resists to treatments, in particular medication. Moreover, cognitive and cerebral mechanisms underlying this food avoidance are very little known. Therefore, research to understand these functional bases is essential. For this, we would like to highlight by the study of gaze control a behavioral marker of active avoidance, and design paradigm which validate tasks and measurements that could characterize Anorexia Nervosa. For this purpose, we tested the patients, based on two distinct profiles, restrictive and bulimic (with periods of purging). Each group is composed of n=30 patients. The behavioral marker of food avoidance has been identified with an eye-tracker during the realization of three tasks based on food pictures items. The results of the patients were compared with those of matched healthy controls (n=30). First, subjects had to evaluate the health and hedonic value of each item. Then, choose between two foods based on their preferences. Finally, the maximum amount they would be willing to eat for each food. Differences were observed between the distinct patients profiles in their food preferences and choices. Furthermore, the choice context brought patients to express attention bias toward low caloric items, and made patients to accept foods that they would never have accepted. Lastly, results of this study will allow us to develop a tool for early diagnosis and phenotyping, but also, targeted and profile-specific cognitive-behavioral therapies.

Keywords: Eating disorder, Anorexia Nervosa, Anxiety, Visual attention bias, Gaze control, Aversive avoidance, Cognitive therapies, Food decision-making, Phenotyping.

Title: Lateralized perception of static and dynamic social interactions in left and right visual cortex

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Abstract:

The visual system has extensively been studied in relation to its function in object and action recognition. Latest research findings shows that it also plays a specific role in representing social interactions (an agent acting towards another), hosting specialized neural structures for this task. In current studies, static representations of social interactions (two people facing towards *vs.* away from one another) and dynamic representations (video-clips of interacting/non-interacting people) yielded stronger activity for facing/interacting in left extrastriate body area (EBA) and right posterior superior temporal cortex (pSTS), respectively. We asked whether different localization and lateralization of the effect might depend on the stimuli being static or dynamic. We reanalyzed two fMRI datasets, where the same 15 female and male adults saw video-clips and static images of facing –seemingly interacting– and non-facing people. First, whole-brain analysis replicated higher activity for facing (*vs.* non-facing) bodies in visual cortex, which was overall stronger for dynamic stimuli. For both static and dynamic stimuli, the effect was stronger in left areas. Next, we individually localized the body-selective EBA, the motion-selective MT/V5, the biological motion-selective pSTS, the so-called social-interaction pSTS (SI-pSTS) –and other (control) visual areas. Region-of-interest analysis showed that the *facing>non-facing* effect in EBA occurred for both static and dynamic stimuli, and was stronger in the left. MT/V5 and pSTS showed the same left-lateralized effect but only for dynamic stimuli. The SI-pSTS showed a third response pattern with a selective, bilateral effect for dynamic stimuli. Challenging the common view that allocates *social stuff* to right visual areas, these results support a prominent role of left regions in social-interaction processing. Moreover, they suggest that within the *hub* for social processing in pSTS, there are two different regions, biological-motion pSTS and SI-pSTS, with different response profiles, and presumably different functions in the representation of socially related/interacting agents.

Gaze and trajectory in landmark-based navigation

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Navigation is a crucial skill for both humans and animals as they explore their surroundings. Humans heavily depend on vision, utilizing visual landmarks to navigate through complex environments. In the present research, rhesus macaques are employed as an effective model for examining landmark-based navigation. The objective is to investigate the gaze and trajectory patterns in both landmark-based and non-landmark environments. To achieve this, a virtual arena featuring three landmarks is utilized; and in certain trials, these landmarks are intentionally occluded. We have mapped the spatial gaze patterns in both landmark-based and non-landmark environments to analyze the animals' navigational behavior in using the landmarks within the virtual arena. Our preliminary data show that gaze patterns are distributed between landmarks and the floor of the arena suggesting that animals do learned to rely on the geometry of the environment in addition to landmarks.

Test – retest reliability of a skewed gambling task

Background

Skewness in gambling refers to the distribution of reward outcomes. Gambling games such as slot machines and lotteries are typically characterized by skewed gambles, and their profitability suggests that people are naturally attracted towards these skewed gambles. Yet, surprisingly, very few neuroimaging studies in the gambling literature have studied skewness. To this aim, we developed a refined and ecologically valid version of a skewed gambling task (SGT) with a parametric design that systematically varied the following key parameters: expected value, variance, and skewness.

Objective

In the field of neuroscience, the importance of examining the test-retest reliability cannot be overstated. Ensuring that a task consistently measures the same underlying construct across different testing sessions is crucial for the validity and interpretability of research findings. Thus, we conducted a pilot study to examine test-retest reliability of our refined SGT.

Method

Twenty-six healthy adults participated in the SGT across two online sessions, ten days apart. We analyzed reliability of both summary statistics and parameters from computational models using Pearson's correlations and intra-class correlations.

Results

Reliability of summary statistics was moderate to good (0.48-0.73). Computational model parameters showed moderate to excellent reliability (0.5-0.75), except for variance, which was below the accepted threshold (<0.4).

Conclusion

In sum, measures from SGT demonstrate moderate to good reliability. Importantly, skewness parameter which is the primary interest of this task showed excellent reliability.

NeuroFrance abstract *2500 char max (with tab)*

Marion Ducret

Title (capital letters, 350 characters max):

THE NEUROPHYSIOLOGICAL BASIS OF LEARNING TO LEARN IN MACAQUE MONKEYS

Learning to learn is a separate function from classical learning, which makes our learning more efficient and flexible. It has been particularly associated with primate species (Harlow, 1953), and lesions disconnecting lateral prefrontal cortex (LPFC) in macaque monkeys lead to a selective loss of this ability (also referred to as Learning Set), whilst sparing simple learning (Browning et al., 2007). LPFC forms an interacting circuit with the midcingulate cortex (MCC), and the MCC plays an important role in error/reward and performance evaluation (Procyk et al., 2016), necessary steps in efficient learning. Most electrophysiological recordings are made after extensive training of the animals, so recordings are made ***after*** animals have learned to learn on the task, thereby completely ignoring neurophysiological changes that permit learning to learn. This project will identify these crucial changes thanks to a longitudinal recording approach, starting with task naïve animals. We recorded a monkey with 256 chronic intracortical electrodes (FMA, Microprobes): 64 in the LPFC and 64 in the MCC across both hemispheres. The monkey performed two tasks on a touchscreen with eye movement monitoring. In the first "task" with very little cognitive demand, the Check Touch Object task, the monkey maintained touch on a lever for a delay and then touched a target that appeared to obtain reward. The second task was Object Discrimination learning, in which monkeys learn which of a pair of concurrently presented objects is rewarded, for a large number of pairs presented serially. This classical learning task has a higher cognitive demand and provides scope for learning to learn. Our aim was to investigate the longitudinal changes in the neural correlates of choices and feedback processing before, during, and after the animal learned to learn. We performed muti-unit activity and local-field potential analysis and compared the two tasks to highlight which neurophysiological characteristics are present prior to learning, and which are put in place during the learning phase. We found that correct and incorrect feedback responses are undifferentiated at the very first stages of learning and we showed the pattern of differentiation between them as the learning progresses. The work here represents the start of a larger effort to better understand keys of learning optimization through learning to learn.

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.

Jacopo Baldi Institut Sciences Cognitives

Neuronal activity in prefrontal and ventral premotor cortex linked to social affiliative behaviors in free-moving macaques

Neurophysiological work has shown that neurons in premotor and prefrontal regions of macaque monkeys respond to motor action goals performed with different effectors (i.e. hand and mouth), as well as to social stimuli within the visual and acoustic domain. Notably, studies in macaques and marmoset have demonstrated that the behavioral context of heard vocalizations influences the neuronal activity in these regions. Historically, electrophysiological studies in nonhuman primates have involved the restraining of the animal, limiting its movements and therefore the repertoire of behaviors it could produce. This has been an evident obstacle to reliably studying the neural correlates of spontaneous, ecological behaviors, especially for physical and auditory social interactions. We built an experimental platform (EthoCage) involving a large enclosure in which we recorded wirelessly the neuronal activity of freely-moving macaques (alone or in pairs), while their behavior was tracked by a system of cameras and microphones. This experimental setup allowed us to acquire data on a wide range of ecologically-relevant behaviors.

The first goal of this study was to investigate the neuronal activity in the ventral premotor cortex (F5) and in the dorsolateral prefrontal cortex (45a, 46v) during socially relevant spontaneous physical interactions between pairs of monkeys. We recorded from 128 channels chronically implanted in each of two individuals. The individuals were performing hand and mouth actions aimed at different social and non-social goals (i.e. allo-grooming, self-grooming, foraging).

The second goal was to study in the same areas the encoding of auditory interactions. We recorded from individuals alone in the EthoCage, and played back vocalizations. For both social interaction modalities, we found interesting significant modulations of the single- and multi-unit activity in both regions. Preliminary data indicate that there is an encoding of the social context of motor actions, and that behavioral context affects the neural correlates of vocal exchanges. These finding highlight the importance of a new ecological approach to neuroscience in order to uncover new brain functions.