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ABSTRACT BOOK

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List of posters in alphabetical order
(Page number = Abstract/Poster number #)

The role of Astrocytes in post-traumatic stress disorder

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Post-traumatic stress disorder (PTSD) is a complex psychiatric condition characterized by intrusive symptoms and heightened emotional reactivity following exposure to traumatic events. An intriguing aspect of PTSD is the alteration of memory, where specific aspects of the trauma are excessively remembered while the overall context is often forgotten. This research project focuses on investigating the neurobiological basis of this alteration, specifically targeting the GMES signaling pathway. Preliminary findings indicate that a high dose of corticosterone CORT induces a decrease in astrocyte viability through PAI-1 inhibition, thereby promoting pro-BDNF accumulation and activating apoptotic pathways. Astrocytic cultures exhibit a significant decrease in viability after CORT treatment, prompting an in-depth study of the underlying causes through apoptosis assays, proteomic analyses, and morphological studies. In a murine model of PTSD, freezing behavior is assessed in WT and PAI-1 KO mice to elucidate the role of PAI-1. Results demonstrate that WT mice develop PTSD-like behavior with fear conditioning test, which is attenuated in PAI-1 KO mice. Additionally, astrocyte quantification confirms astrocytic apoptosis in the PTSD model, supporting the hypothesis of decreased astrocyte numbers. The transition from normal to pathological stress via GMES dysregulation underlies the PTSD profile. The accumulation of pro-BDNF induced by this cascade could lead to apoptosis in brain regions rich in glucocorticoid receptors such as the hippocampus, thereby contributing to PTSD pathogenesis. These findings could pave the way for novel therapeutic interventions targeting the GMES cascade for PTSD treatment.

Perception Census: Linking colour preferences and colour-emotion associations

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Colours are frequently linked to different emotions. They help us perceive emotions from others' faces and carry significant symbolic meanings (e.g., national colours). They might also help us interpret the affective meanings behind man-made objects and spaces. Furthermore, colour also impacts our daily activities and shapes our personal preferences and choices (e.g., choice of black furniture or clothing). Indeed, research shows that humans have stable colour preferences and associations with emotion concepts. Despite separate studies on these two phenomena, as far as we know, no research has investigated their relationship. It seems logical, that we would associate positive emotions with colours we like and vice versa. Nevertheless, this hypothesis has not been examined, and there are reasons to suspect that this might not be the case. Some colours show congruency in attributed valence: i.e., blue is a commonly liked colour and is associated with positive emotions such as calmness or contentment, similarly brown is a disliked colour, and is associated with negative emotions like sadness or disgust. Other colours, like yellow or pink, show incongruency in attributed valence, as they are commonly disliked, yet associated with positive emotions. Our study aims to examine the valence congruency between colour preferences and colour-emotion associations on individual level, by using the data acquired through the international Perception Census project (https://perceptioncensus.dreamachine.world/). Two separate online tasks investigated colour-emotion associations (Geneva Emotion Wheel) and colour preference (Colour Picker). They were completed by 31,308 and 36,757 participants respectively. We are now analyzing the results, to understand the relationship between color preferences and colour-emotion associations, hoping that this will help us understand the role of emotional valence in these two affective phenomena. These results will contribute not only to colour research but also to broader approaches that study human affective processing, especially on the different types of valence.

A longitudinal assessment of early sensory development and social visual attention in 24-48 months old toddlers with autism spectrum disorder

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Introduction: Sensory processing affects 90% of individuals with ASD and is strongly implicated in social cognition. Individuals with ASD often exhibit social behaviors characterized by impairments in communication, eye contact, and joint attention. These difficulties are measurable during the first year of life in infants later diagnosed with ASD.

Research Questions: (1) Do sensory difficulties at the time of diagnosis predict the severity of ASD symptoms? (2) Is joint attention a predictive factor for the development of social communication in ASD? (3) How does the association between sensory processing difficulties and deficits in social cognition evolve during development? (4) Are the sensory difficulties together with joint attention impairment determining in the social communication deficit in ASD?

Methods: Protocols 1 and 2 are naturalistic eye-tracking paradigms designed to measure different aspects of joint attention involving the child and parent (protocol 1), the child and clinician (protocol 2). Protocol 3 measures sensory behaviors with EEG and observational assessments.

Hypotheses: 1) sensory particularities interfere in the development of social communication 2) social communication deficits are associated with joint attention impairment 3) a correlation will be found throughout the study between sensory processing difficulties, social communication deficits, and joint attention dysfunction.

Conclusions: Longitudinal measures will contribute to the study of sensory and social dimensions of ASD post-diagnosis which could have significant clinical implications in the current and early intervention of ASD.

Fecal Microbiota Transfer reduces alcohol preference in stressed rats

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Alcohol use represents a significant health concern, accounting for 4.5% of global disease burden. Only a small proportion of individuals develop persistent alcohol used disorder though. With current pharmacotherapies largely unsatisfying, discovering novel alternatives to prevent alcohol use disorder becomes a priority. Hence, identifying biological markers predicting vulnerability to develop excessive alcohol consumption may lead to real improvement of clinical care. Converging evidence suggests that gut microbiota is capable of influencing immunity, brain and behavior. We thus investigated gut microbiome and signs of peripheral inflammation in stressed rats exhibiting uncontrolled alcohol seeking behaviors defined as: 1) Inability to abstain during a signaled period of reward unavailability, 2) Increased motivation and 3) Persistent alcohol seeking despite aversive foot shocks. Compared to controls, rats exposed to chronic stress during adolescence exhibited impulsive, inattentive and disinhibited behaviors. After 33sessions of daily alcohol (10%weight/volume) self-administration, all rats were screened according to the 3criteria defined above. Majority of the vulnerable group was composed of stressed rats, and most of the resilient group was composed of controls, confirming that stress during adolescence increases the vulnerability to develop AUD-like behavior. All rats were then given access to 2sources of reward: 10%w/v ethanol and saccharine (0.2 %, 0.00625%, 0%), 2consecutive sessions for each concentration, during which stressed rats exhibited a clear-cut preference for alcohol compared to controls. Strikingly, we identify a long-lasting peripheral inflammation in stressed rats (CCL5, IL-4). Not only fecal microbiota transfer lowered stressed rats' preference for alcohol but it restored inflammation modulators levels to those observed in controls.

Exploring the impact of the partial NDMA receptor agonist D-cycloserine on cognitive flexibility and NMDA receptor signaling hub components in Shank2-deficient mice

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Neurodevelopmental disorders such as autism spectrum disorder (ASD) have a heterogeneous etiology but are largely associated with genetic factors. Robust evidence from recent human genetic studies have linked mutations in the Shank2 gene to idiopathic ASD. Modelling these mutations in animal models of Shank2 recapitulates behavioral changes, e.g., impaired social interaction and repetitive behavior of ASD patients. Shank2-deficient mice also exhibit NMDA receptor (NMDAR) hypofunction and associated behavioral deficits. Of note, NMDAR are strongly implicated in cognitive flexibility. Their hypofunction, e.g., observed in schizophrenia, or their pharmacological inhibition leads to impaired cognitive flexibility. However, the association between Shank2 mutations and cognitive flexibility is poorly understood. Using Shank2-deficient mice, we explored the role of Shank2 in cognitive flexibility measured by the attentional set shifting task (ASST) and whether ASST performance in Shank2-deficient mice can be modulated by treatment with the partial NMDAR agonist D-cycloserine (DCS). Furthermore, we investigated the effects of Shank2 deficiency, ASST training, and DCS treatment on the expression level of NMDAR signaling hub components in the orbitofrontal cortex (OFC), including NMDAR subunits (GluN2A, GluN2B, GluN2C), phosphoglycerate dehydrogenase, serine racemase. Surprisingly, Shank2 deficiency did not affect ASST performance or alter the expression of the investigated NMDAR signaling hub components. Importantly, DCS significantly improved ASST performance, demonstrating that positive NMDAR modulation facilitates cognitive flexibility. Furthermore, DCS increased the expression of GluN2A in the OFC, but not that of other NMDAR signaling hub components. Our findings highlight the potential of DCS as a pharmacological intervention to improve cognitive flexibility impairments downstream of NMDAR modulation and substantiate the key role of NMDAR in cognitive flexibility. Work supported by DFG.

Neural decoding of temporal features of Zebra Finches Song

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Auditory decoding of temporal features is a complex process in which vocalizations such as birdsongs are segmented into distinct auditory units, a crucial step in transforming sound into meaning. The songbird auditory system offers a valuable model for studying the neural representation of complex sounds. The hierarchical structure of the Zebra Finches' song makes it ideal for in-depth analysis of auditory decoding.

We use stacked Bidirectional Long Short-Term Memory (BiLSTM) deep neural networks to decode the amplitude envelope and the time-locked envelope features of zebra finch songs. To assess the neural activity's efficacy at segmenting continuous songs into units and decoding amplitude, the network was trained with local field potential (LFP) and multi-unit activity envelope (MUAe).

In ensemble responses, both the amplitude envelope and time-locked features could be accurately decoded using LFP and MUA. The performance of LFP and MUAe was very similar, but MUAe gave slightly better results for envelope decoding. It was observed that temporal information might not have been present everywhere in the brain/auditory pallium, and this segmentation function could be modulated by other factors (such as attention). Notably, the envelopes of the introductory notes and the first motif were significantly better decoded than the second motif. This result suggested that these specific parts of songs were receiving more attention. Additionally, network accuracy and inter-trial phase coherence exhibited a positive linear relationship in LFP and MUA signals, indicating the importance of neural synchrony.

High-performance decoding of temporal features has shown how neural representations of these features facilitate or reflect the segmentation of songs. It provides valuable insights for future research into the intricate processes involved in vocal communication.

Modulating the protonmotive force of astrocyte mitochondria: effects on neuronal function

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Astrocytes play a pivotal role in neuronal survival and function by supplying neurons with energy in the form of lactate. The transfer of lactate from astrocytes to neurons (known as the Astrocyte Neuron Lactate Shuttle), has neuroprotective effects. Increase in lactate production can be achieved by activation of mitochondrial uncoupling proteins, which slightly depolarize astrocytes and decrease the mitochondrial proton motive force (PMF). In a mouse model of Alzheimer's disease, our lab showed that this decrease in PMF is beneficial to prevent hippocampal and dendritic atrophy, reduce aberrant neuronal electrical activity, and improve memory.

To achieve rapid, reversible, and cell type-specific modulation of PMF, we aim to act on PMF optogenetically using novel toolkits which specifically target mitochondria in astrocytes. The first tool, mtOFF, pumps protons into the matrix and is activated by orange light. Activation of mtOFF decreases mitochondrial matrix pH and PMF, increases oxygen consumption, and reduces ATP production. Conversely, we use mtON, a proton pump oriented in the opposite direction, that pumps protons out of the matrix, hyperpolarizing the mitochondria upon exposure to light and producing an opposite effect.

We developed adeno-associated viral vectors with astrocytic promoters for mtON and mtOFF expression and confirmed their colocalization with mitochondria in astrocytes in primary cell cultures. Our next step is to optimize the optogenetic setup in primary astrocyte culture, followed by further examination in neuron-astrocyte co-culture and acute brain slices. These findings will illustrate the role of astrocytic PMF in neuronal networks and open therapeutic opportunities for neurodegenerative diseases.

Can a single sensor measure hip range of motion in hip osteoarthritis patients?

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Hip range-of-motion (RoM) is an important outcome for total hip arthroplasty (THA) patients. While typically assessed in clinics, its measurement during daily activities (ADL) remains unexplored. This study aims to determine if using a single wearable inertial measurement unit (IMU) on the thigh accurately measures hip-RoM in hip osteoarthritis patients.

Patients were recruited pre-surgery and scheduled at 3-months and 1-year post-surgery, along with five healthy subjects. The analysis included 15 pre-surgery, 8 three-month post-surgery, and 4 1-year post-surgery patients. 10 gait trials at comfortable speed were recorded using a motion capture system (MCS) and a thigh-IMU. Hip-RoM was calculated through the MCS, while thigh-RoM was calculated by aligning the IMU with manual-functional calibration and integrating its angular velocity. A multi-linear-regression model, selected through leave-one-out cross-validation, used thigh-RoM and biomechanical and IMU-derived features to predict hip-RoM. Features were chosen based on Pearson's correlation to assess importance. Considering that errors of 2°-5° are clinically acceptable for joint angles, we assume acceptable differences of 4°-10° for RoM. Bland-Altman limits-of-agreement within 20° will be considered acceptable with minimal bias.

The median absolute error between IMU and reference hip-RoM was 4.6±6.1°, and limits of agreement were between -12.9 and 13.1° with a bias of 0.1°.

These results do not completely validate using a single thigh-IMU in measuring hip-RoM with Bland-Altman limits-of-agreement between -10 and 10°. The linear pattern in the Bland-Altman analysis suggests potential improvement using deep learning models since regression was insufficient. This could enable objective evaluation of THA patients during ADL.

Potential for white matter microstructure quantification on a clinical 7T system

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Introduction : dMRI examines tissue microstructure non-invasively. While 7T MRI systems equipped with stronger gradients offer higher signal-to-noise ratio and more flexible diffusion encoding, challenges like spatial distortions and uneven excitation hinder its full potential. Here we aim to first evaluate the feasibility of WM microstructure quantification at 7T and second investigate the impact of acquisition protocol on model parameter estimates.

Methods: 5 healthy volunteers underwent a brain scan on a clinical 7T MRI system. DWI images were acquired using the following protocols: *b*3 protocol [N=4]: b ms/µm2](dir)=0(4), 1(20), 2(40), 3(60), TE=78 ms, 1.5-mm3; *b*13 protocol [N=1]: b [ms/µm2](dir)=0(6), 1(12), 2.5(30), 6(60), 13(90), TE=115 ms, 2-mm3. Pre-processing included: NORDIC denoise, Gibbs ringing correction, susceptibility and Eddy current distortion correction. WM microstructure parameters were estimated using the Standard Model (SM) framework. The relationship between model parameters was assessed within each protocol, both region-wise across WM and voxel-wise within the internal capsule (IC). Moreover, individual parameter maps (N=1) were compared to average parameter maps (N=4) using the *b*3 protocol to evaluate the robustness of the estimated model parameters.

Results: Single-subject parametric maps were smooth and consistent with values reported at 3T, even at 1.5-mm isotropic resolution. There was a strong dependence of parameter estimates on the acquisition protocol. Moreover, voxel-wise and ROI correlations between model parameters remain consistent among subjects at *b*3 and are reinforced at the *b*13 protocol.

Discussion and conclusions: SM parameter maps at 7T confirm the feasibility of high resolution microstructure quantification using an HCP-like protocol, with a higher spatial resolution than the one typical of 3T data. Ultra-high b-values challenge SM assumptions of Gaussian compartments and stick geometry, introducing strong correlations between SM estimates, but could give access to quantification of more advanced microstructure features like axon diameters.

Transcriptomics analysis of inflammation in Alzheimer's Disease

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Alzheimer's disease (AD) is characterized by progressive accumulation of Amyloid Beta (Aβ) and Tau triggering a pathological inflammatory reaction by astrocytes and microglia, leading to neuronal death.

Here, we are investigating the human brain's adaptive response to AD progression by examining the RNA dynamics in 30 fresh-frozen human post-mortem hippocampal samples, divided into three groups of non-neurological controls (CT, n=6), early AD (EAD, Braak 4 and 5, n=12), and late AD (LAD, Braak 6, n=12). We analyzed 770 RNA strands related to neuroinflammation and studied central inflammation, peripheral immune infiltration and oligodendrocyte related pathways using cell deconvolution and protein studies.

Comparing RNA levels between the groups showed increasing differentially expressed as the disease progresses. Neuronal cell deconvolution performed on subsets of those genes revealed that neuronal genes were stable in EAD and downregulated in LAD, astrocyte genes were continuously upregulated, microglial genes were upregulated in EAD and stayed stable in LAD while oligodendrocyte genes were downregulated in EAD and came back to CT levels in LAD. CCL2, a gene responsible for peripheral immune infiltration in the CNS, was identified as negatively correlated with oligodendrocyte genes while positively correlated with microglia and peripheral immune cells present in our samples. Immune cell deconvolution showed a decreased CD4+ T-Cells and NK Cells presence and an increased CD8+ T-Cells presence in LAD.

In this study, we show that the inflammatory response initially affects oligodendrocytes in EAD, then shifts towards an inflammation impacting neurons in LAD while oligodendrocytes return to normal.

Birth-date specific plasticity of cortical neurons

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Cortical neuron diversity starts pre-mitotically at the progenitor stage by a series of temporal processes, but evidence show that identity is refined through cell-extrinsic processes post-mitotically. To what extend the micro-environment of a post-mitotic neuron contributes to shaping its identity remains unclear.

To address this question, we challenged the laminar position of early born neurons (E13.5) and late born neurons (E15.5)- isolated by isochronic labelling with FT [6] -by transplanting them in a novel cortical environment. We assessed their identity before and after transplantation, in relation to their birthdate and laminar position, by looking at their molecular, transcriptomic, electrophysiological, and morphological profile.

By first performing scRNAseq of the donor cells we found that newly born neurons are mostly undifferentiated at the time of the transplantation, going along with previous studies. We then performed patch-sequencing of transplanted neurons integrated in different cortical layers and found a birth-date specific plasticity of transplanted neurons. Early-born neurons seem to acquire diverse transcriptomic identities based on their laminar environment while late-born neurons seem restricted to a superficial layer fate. To further investigate this, we aim to investigate epigenetic conformation of cells before transplantation.

Brain activation for language and its relationship to cognitive and linguistic measures: a multimodal exploration

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Language requires complex skills, from auditory perception to higher-order syntactic planning. The neural bases of these abilities have been mostly investigated separately so far. Here, we employ data-driven multimodal and multivariate analysis methods to characterize language learning profiles in a large dataset in which a broad array of behavioural and brain imaging data was collected, with the aim of identifying the key dimensions underlying language learning, their subcomponents and their relationship with language-related brain activation.

Participants (N=134) differed in their multilingual experience, and a subgroup (N=25) had a previous dyslexia diagnosis. Behaviourally we assessed cognition, domain-specific measures and language-specific tests, and fMRI data assessed speech processing in their first language. Partial Least Squares Correlation was used to uncover common dimensions underlying the two data modalities (i.e. behavioural data and fMRI data).

The PLS analysis in the whole sample revealed one significant component, explaining 34% of the variance. The component was positively correlated with performance on higher-level general cognitive measures and language tasks. In the neural data, this component was associated with greater brain activation in predominantly bilateral anterior temporal and inferior parietal areas. In the analysis that included only the typical readers, 3 significant components were revealed.

The present work reveals both associations and dissociations between key dimensions underlying language. Overall, there is a substantial overlap in the behavioural measures between linguistic and cognitive skills. Moreover, there were more components in typical readers, potentially suggesting better segregation of function and possibly greater neural and behavioural specialisation in healthy readers.

Language aptitude, cognition, fMRI, multilingualism, dyslexia

Exploring the role of sleep in the learning of a goal-directed sensorimotor task

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Rodent learning tasks used to assess memory consolidation during sleep prevalently involve an overnight learning experience e.g. fear conditioning.

Here we study a progressive learning paradigm to address how sleep's adaptive and memory consolidating roles affect the animals' learning performance.

We chose a two-tone auditory discrimination task that required head-fixed and water-restricted mice to actively discriminate between a Go- (8 kHz) and a No-Go (12 kHz) tone to obtain a water reward. The training happened daily at Zeitgeber times ZT2-6. After becoming experts, the tone contingencies were reversed. This experimental design allowed us to separately study the roles of sleep across the different phases of the task, from the moment of water restriction ("WR") to pure rule learning during reversal training ("RT"). Spontaneous sleep/wake was recorded in freely-moving conditions at the end of the task and in the following dark phase (ZT6-12 and ZT12-24).

Mice became experts in the task over 7-14 days, as assessed by means of their discrimination index (chance level performance: d-prime=0, expert performance: d-prime>1.5). Across days, mice improved by reducing the False Alarm rate, which corresponds to licking in response to the No-Go tones, and by suppressing unspecific licking ahead of stimuli.

At the end of the training, the d-prime had become significantly more positive with respect to the first day of training (paired t-test, p =0.0003) for all the mice.

As the animals progressed in the experimental protocol, we observed changes in their sleep-wake pattern. Compared to the pre-water-restriction baseline ("BL"), the acute removal of the water bottle for 24 h ("WR") did not affect the time spent in NREMS and REMS (N=8 mice, paired t-test, p=0.24 for NREMS, p=0.58 for REMS). However, at the moment of the first exposure to the setup (free-licking, "FL"), the mice spent significantly more time in both NREMS and REMS during the dark phase (paired ttest, p=0.00035 for NREMS, p=0.00016 for REMS). We are currently analyzing the sleep at the moment of forward and reversal training ("FT" and "RT"). Together, our work is a first step towards understanding the adaptive learning of sleep to daily learning experiences.

A NOVEL MRI-COMPATIBLE RESTRAIN SETUP FOR AWAKE RAT MULTIMODAL EXPERIMENTS

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Over the last few years, substantial research efforts have been directed toward the field of awake fMRI in preclinical rodent models. The spread of high-field preclinical scanners as well as the translational potential of fMRI data make this a critical topic for neuroscience. However, because MRI is highly sensitive to movement, animals' awake recordings remain a challenging task. Nowadays, head-fixation systems are the most common method to address the problem, as anesthesia strongly affects brain function. Although numerous effective constriction setups are available for mice, a user friendly and durable rat restrain system is still lacking. In this study, we present a noninvasive body and head restrain setup for conducting awake rat functional magnetic resonance imaging (fMRI) . The setup presents several key advantages. Firstly, its design eliminates the need for a nose cone, thereby creating additional space for incorporating multiple other recording techniques, including optogenetics, fiber photometry, and pupillometry. Secondly, its compactness enables seamless adaptability to rats of all sizes without requiring any modifications. Additionally, the system's adjustable positioning, facilitated by a sliding mechanism, guarantees compatibility with every MRI cradle.

Our preliminary findings indicate that the implant's minimal invasiveness contributes to the absence of distress or anxiety symptoms in rats. Additionally, the implant demonstrates stability over a two-month duration. Moreover, initial awake recordings exhibit promising outcomes concerning the system's resilience and effectiveness, effectively mitigating movement in all dimensions.

Brain-wide neural dynamics underlying fast goal-directed reward-based learning

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Animals have the remarkable ability to adapt their behaviour to novel situations and quickly respond to external stimuli using associations already encoded in the brain. While brain areas are usually thought to have functionally distinct contributions during goal-directed behaviour, it remains unclear how the brain as a network of areas enable rapid learning. Here, we developed a behavioural paradigm that allows us to probe rapid reward-based sensorimotor learning in mice, overcoming the limitations of longitudinal recordings. Mice are first pretrained on an auditory detection task and, once expert, are transferred to a whisker-based tactile detection task. First, we observed that mice
learn the new whisker-reward association in minute timescales and go from novice to expert performance levels within a single session. Second, this learning is reward-dependent and often requires few trials to emerge. During this single-session learning, we performed brain-wide simultaneous Neuropixels recordings across multiple cortical and subcortical brain areas aligned to a reference atlas. We observed widespread task-related neural activity across multiple areas beyond those that are canonically involved in a whisker detection task. Further, specific neuronal populations showed reward-dependent changes in representations upon trial-by-trial learning. Our results suggest brain-wide neuronal activation during minute-timescale learning and future work will
investigate changes in inter-areal interactions.

Investigating the Interaction Between Bodily and Environmental Sensory Stimuli

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The human brain constantly processes a myriad of sensory stimuli, both from the external environment and internal bodily states, such as heartbeats and respiratory signals, which are crucial for homeostasis and survival. Our research focuses on designing an innovative and naturalistic experiment to explore how these external and internal sensory inputs interact within the brain. We aim to elucidate the impact of this interplay on both behavioral responses and neural activity, providing insights into the mechanisms underlying sensory integration.

Longitudinal Dynamic fMRI Analysis of Music vs Singing Perception in Preterm Infants

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Despite similarities, music and singing are perceived differently with distinct neural processing in the brain. Though both involve musicality, singing incorporates a vocal component. The origins of this distinction during neurodevelopment are unclear. With newborns already able to distinguish speech from music, the preterm population offers an opportunity to study the ontogenesis of this processing distinction even earlier in development. 54 very preterm infants at the University Hospital of Geneva, Switzerland, underwent task-based longitudinal fMRI at 33- and 40-weeks gestational age (GA) while infants listened to a melody either played by a flute or sung by a female voice. After removal for excessive motion and incomplete scans, the cohort comprised 44 preterm infants at 33-weeks and 46 at 40-weeks. A dynamic psychophysiological interaction of co-activation patterns approach (PPI-CAPs) was then applied. This approach selects moments when a seed region (auditory cortex) is highly active, and clusters frames based on their co-activation patterns (CAPs). Each CAP is then tested whether it varies according to the seed activity, task, or interaction between the two (PPI-effect). ICA-derived functional networks were overlayed to assign functional relevance to the CAPs. Results showed early musical signatures at 33-weeks GA, with emotion-linked regions activated during music at both time points and the salience network active during singing at both time points. Present only at 40-weeks GA, we saw developmental novelty, with visual activation during the music stimulus and sensorimotor activation during the singing stimulus, suggesting the development of a multisensory response during this early stage of development.

Neuronal Plasticity after Spinal Cord Injury: Unraveling extracellular matrix dynamics

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Spinal cord injury (SCI) leads to varying degrees of sensorimotor deficits in patients. However, spontaneous recovery usually occurs during acute phase after the injury, but plateaus in subacute phases. We have modeled this in a mouse model of SCI, and locomotor assessments show spontaneous motor improvements occur between 3 days and 21 days post-injury, but the recovery plateaus at 3 weeks with no further improvements, even tested at 3 months post-injury. Immune cells such as microglia and astrocytes are thought to play a crucial role in spontaneous recovery and anatomical alterations. This has been studied extensively at the lesion site but how immune cells regulate neuronal plasticity caudal to the injury site is poorly understood. This project is based on investigating how immune cells modulate extracellular matrix (ECM) components, which are involved in neuronal plasticity. Preliminary results show that after SCI, expression of ECM components and immune cells are highly perturbated in the spinal cord distal to lesion site. We hypothesized that by modulating the immune cells and extracellular matrix components, we could improve spontaneous recovery and furthermore trigger new spinal reorganization at a chronic stage, thus resulting in a better functional outcome.

Sensitivity to disgust predicts immune response when exposed to a virtual infection entering the peripersonal space

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Disgust is a pivotal component of the behavioral immune system. It functions as a robust defense mechanism against pathogens, compelling individuals to instinctively avoid repugnant stimuli, thereby potentially bolstering immune defenses at a behavioral level. This reaction is thought to be evolutionarily advantageous, as it reduces the likelihood of pathogen contact and infection. Following exposure to a pathogen, the immune system is expected to respond rapidly. Already the mere visual exposure to infectious threats in virtual reality can elicit an immune response. Here we analyzed the interplay between disgust and immune response signaling factors and brain activity in 2 cohorts of subjects exposed to virtual infections. We show that the immune responses correlate with individual susceptibility to disgust . That is, people who are more prone to disgust tend to elicit lower immune responses (measured through ILC1 activation markers) than subjects who have low disgust scores. We were able to explain such result by modelling the statistical relations between virtual exposure, signaling factors and disgust scores. Additionally, exposure to infectious avatars in virtual reality modulates hypothalamic activity before compared to after exposure. Strength of connectivity between the hypothalamus and visual areas correlate with individual susceptibility to disgust. Altogether, these findings suggest that high-level personality traits such as individual susceptibility to disgust play a key role in mediating anticipatory immune responses, by modulating a signaling cascade starting in regions associated with the salience network, involving HPA related signaling factors and lastly in the ILC activation markers measured in the blood.

Evidence for somatomotor cortex recruitment during autobiographical memory retrieval

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The retrieval of meaningful events from one's life is a key component of autobiographical episodic memory and can give rise to the sense of reliving the original event (i.e., autonoetic consciousness (AC): Tulving, 1972;1985). However, the behavioral and neural mechanisms underlying AC are still poorly understood. At the neural level, it has been suggested that AC is mediated by the reinstatement of cortical regions that were engaged during encoding (Gilmore at al. 2021; Bone et al., 2020; Staresina et al., 2013). While previous research focused predominantly on the reinstatement of auditory and visual stimuli in the respective cortices and the hippocampus (Gordon et al., 2014; Daselaar et al., 2008; Wheeler et al., 2000), the motor and sensory cues of the person while encoding the event, have not been investigated. Here, we postulated that primary motor cortex (M1) would be reengaged at retrieval through hippocampal-neocortical trace reactivation (Sekeres et al., 2018). Through an immersive 3D virtual reality (VR) experimental paradigm we had participants (N = 30) encode new real-life like events in the laboratory. We then recorded 3T fMRI while participants were asked to relive each of these events 24 hours after the encoding process. We observed an increase in M1 activity (alongside classic memory regions) during free reliving, as well as an enhancement of hippocampal connectivity with left M1 and S1, suggesting that re-experiencing past events also involves the reenactment of associated motor actions.

Movement coordination via a cortico-ponto-thalamic loop

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Movement and locomotion are governed by highly specialized subcortical motor networks. Many subcortical centers form loops with the cortex and the thalamus. E.g, the cortico-basal ganglia (BG)-thalamocortical loop is crucial for movement control, and disruption of BG activity leads to characteristic, unilateral rotation.
In this study, we investigated whether the pontine reticular formation (PRF) also participates in a motor-related, cortico-subcortico-thalamocortical loop since PRF also sends inhibitory terminals to the intralaminar thalamic nuclei (IL) and parafascicular nucleus (Pf), like BG, both in rodents and humans and the activation of PRF inhibitory fibers disrupts locomotion. We studied the effects of unilateral optogenetic activation of PRF inhibitory cells (PRF/GlyT2+) on locomotor behavior and analyzed the impact of cortical inputs on PRF/GlyT2+ neuronal activity.
We found that layer 5 (L5) neurons of higher-order motor cortical areas exert strong glutamatergic control over the PRF/GlyT2+ neuronal activity primarily via synaptic contacts on dendrites. Using anterograde viral tracing, we found that mid-caliber dendrites and spines of PRF/GlyT2+ cells receive L5 inputs from the frontal cortex (M2 and Cingulate) in RBP4-Cre/Glyt2-eGFP transgenic mice. In vivo, juxtacellular recording showed that photoactivation of cortical L5 cells evoked short-latency APs with high probability in PRF/GlyT2+ cells. The same L5 cells innervated PRF and its thalamic targets. Photoactivation of PRF/Glyt2+ neurons led to a significantly decreased firing rate of the IL/Pf cells and resulted in unilateral rotation and movement initiation.
Our findings suggest that synchronous frontal cortical activity conveys behavioral signals to PRF, and PRF/GlyT2+ cells can transfer this cortical input as an inhibitory signal to the IL/Pf before they return to the cortex via the thalamocortical pathway. Our results suggest that PRF plays an important role in motor control and is part of a larger cortico-subcortico-thalamocortical loop.

Melatonin's Role in Modulating Diurnal Variations of Extracellular Dopamine in CBA/CaJ and C57BL/6 Mice with Distinct Melatonin Profiles

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Melatonin, an indolamine, is derived from the precursor tryptophan through a series of enzymatic steps. In a commonly used strain of C57BL/6J mice, the genes for these enzymes are truncated, resulting in a lack of circadian melatonin rhythmicity. By introducing these alleles, a C57BL/6J congenic line known as CBA/CaJ was created, with the ability to synthesize melatonin. It has been shown that extracellular striatal dopamine (DA) levels fluctuate during the day, as a result of changes in the cholinergic neurons' circadian rhythm activity, which itself would be controlled by melatonin's rhythmicity. As diurnal changes in DA have been shown to alter synaptic connectivity and animal behavior, understanding this modulation has consequences for diagnostics and treatment of neurodegenerative such as Parkinson's disease and psychiatric disorders. In this study, we examined the impact of melatonin (MLT) on evoked DA release using fast-scan cyclic voltammetry (FSCV) in acute striatal slices from CBA/CaJ and C57BL/6J mice. Slices were prepared at two distinct points during the light/dark cycle, corresponding to the lowest and highest MLT levels. Our findings reveal that during the dark cycle, when MLT peaks, DA release decreases in CBA mice and not in C57BL6 mice. Furthermore, when physiological concentrations of exogenous MLT were applied to the slices, it inhibited DA release mainly in CBA/CaJ mice. In contrast, C57BL/6J mice did not display a substantial response, likely due to their reduced sensitivity of receptors to melatonin. Our results confirm that melatonin receptors' activation plays a vital role in modulating striatal DA release and establishing the dose- and time-dependent kinetics of release inhibition and recovery. Additionally, we showed that this regulation of DA rhythmicity by melatonin is mediated through the activity of cholinergic interneurons in the striatum.

Parkinson's Disease: From human-relevant iPSC-derived dopaminergic neuronal models to mechanisms and novel targets.

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Parkinson's disease (PD) is characterized by intraneuronal inclusions of alpha-synuclein (aSyn) known as Lewy bodies (LB). Despite extensive research, the mechanisms governing LB formation remain unclear. Here, we report on the development of a new model that recapitulates the biochemical and morphological diversity of PD neuropathology in human dopaminergic neurons. Using an integrative experimental approach, we demonstrate the power of this model to dissect the mechanisms of pathology formation, conduct drug discovery and target validation studies.

In this model, we employed preformed alpha-synuclein fibrils (PFFs) as seeds to induce the aggregation and formation of LB-like inclusions in iPSC-derived dopaminergic neurons (iDA). Using immunofluorescence, confocal imaging, and correlative light and electron microscopy (CLEM), we demonstrated that our iDA model faithfully captures the ultrastructural and organizational complexities of LBs observed in human PD brains including the sequestration and accumulation of membranous organelles. Our iDA model reproduces the biochemical, post-translational modifications and morphological diversity of aSyn aggregates and inclusions found in human PD brains. Furthermore, it provides a longer time window to investigate the molecular and cellular determinants that influence aSyn pathology aggregation at different stages of pathology formation and maturation.

In this talk, we will present how we have employed this model to gain insights into novel druggable mechanisms underpinning the development and progression of neuropathology in PD and related neurological disorders.

Restoring vestibular function with sensory neuroprosthesis: The vestibulocochlear implant.

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The vestibular system in the inner ear, commonly referred to as the 6th sense, is crucial for balance and spatial orientation. Often unknown, the vestibular system plays a pivotal role in our daily lives: maintaining unassisted postural stability even in challenging situations and preserving visual abilities while in motion. An impaired vestibular system can lead to severe functional limitations, such as chronic imbalance, blurred vision in dynamic settings, and gait disorders. Over 3 million people worldwide suffer from severe vestibular disorders, significantly reducing their quality of life, with no effective treatment available for these patients who are in desperate need of stability.

The vestibulocochlear implant (VCI) is an innovative neuroprosthesis designed to restore both vestibular and auditory functions. It mimics the inner ear's physiological functions, with cochlear electrodes ensuring hearing restoration and three dedicated electrodes sending head movement information directly to the vestibular nerve. After years of development, 24 patients with severe vestibular disorders have been successfully implanted with the VCI. Initial results show significant improvements in vestibular reflexes, especially visual acuity in dynamic settings. This doctoral project aims to evaluate the VCI's functional benefits. Preliminary results indicate positive impacts on gait stability and cognitive functions. This work represents a major step towards transitioning the VCI from a prototype research device to daily clinical practice. It also significantly contributes to the scientific understanding of the vestibular system in both normal and pathological conditions, offering specific outcome measures to guide clinicians and highlighting the synergy of the system's components in maintaining balance.

Microglial activation in the anterior cingulate cortex: a biological marker of early adverse events and future vulnerability to develop alcohol use disorder

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Epidemiological studies have long acknowledged that only a minority of the population is at risk of losing control over alcohol consumption. Aiming at identifying the roots of this vulnerability, ongoing evidence from our laboratory revealed a significant vulnerability to lose control over alcohol consumption in male Wistar rats subjected to a chronic mild unpredictable stress (CMUS) during adolescence. This excessive alcohol seeking behaviour correlated with significant changes in the gut microbiota composition. Most importantly, Fecal Microbiota Transplantation (FMT) from resilient to vulnerable rats not only effectively changed the gut-microbiota composition of receivers, but it also alleviated symptoms of addiction-like behaviours and reduced signs of peripheral inflammation. The present study aims at confirming the effectiveness of FMT to reduce central inflammation as well. Extensive morphological and skeletal analyses converged to identifying an amoeboid shape of the microglia in the Anterior Cingulate Cortex (ACC), but not in the Prelimbic (PRL), of stress rats in contrast to control animals. Current investigations aim at processing brain slices of stress rats post FMT, notably targeting the ACC, PRL and amygdala nuclei. To our knowledge, this is the first set of observations confirming that FMT represent an effective therapeutic strategy for reducing both signs of central/peripheral inflammation and addiction-like behaviour.

The Role of the Transcription Coactivator CRTC1 in Neuroinflammation and Depression

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CREB-regulated transcription coactivator 1 (CRTC1) plays a pivotal role in regulating the expression of genes involved in neuronal survival, synaptic plasticity, and long-term potentiation by interacting with cAMP response element-binding protein (CREB). Our research utilizes a Crtc1 knockout (KO) mouse model, which exhibits increased aggressiveness, depressive-like behavior, and obesity in males.

The bidirectional relationship between obesity and major depressive disorder is well-established, with both conditions linked to elevated neuroinflammatory markers in various brain regions. In the literature, CRTC1 overexpression has been associated with a protective effect against neuroinflammation in the hippocampus. Given the phenotype of our KO mice, we hypothesize that Crtc1 KO males may experience increased neuroinflammation, potentially serving as a triggering factor for depression symptoms and obesity in adulthood.

Preliminary experiments revealed subtle differences in microglia morphology of naïve wild-type (WT) and KO male mice. After immune system stimulation via acute or subchronic lipopolysaccharide (LPS) injections, Crtc1 KO mice exhibited prolonged sickness behavior, with more severe hypothermia within the first 6 hours and higher weight loss on the following days. Additionally, KO mice refrained from voluntary running-wheel activity for a longer period. However, this effect is not due to higher pro-inflammatory cytokine release in the KO mice. Future studies will investigate LPS-induced depressive-like behavior in WT and KO mice, focusing on serotonin/kynurenine pathway imbalances as well as glial cell activity. This project aims to deepen our understanding of CRTC1's role in emotional regulation, neuroinflammation, and metabolic disturbances.

Morphing minds: A preliminary study on derivational morphology in L2 French teaching

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Multilingualism is essential in today's globalized world, yet language teaching practices often rely on theoretical positions without empirical validation. The current experiment is part of a wider research program aiming at contrasting the efficiency of two pedagogical methods in L2 French teaching: the traditional monolingual 'island' method in which teaching focuses on the target language and the pedagogical translanguaging method, which leverages learners' entire linguistic repertoire. The linguistic phenomenon of interest is derivational morphology, i.e., principles underlying word formation through prefixes and suffixes. In order to build controlled materials for this program, we conducted a preliminary study to assess French suffixes' productivity. A total of 12 French suffixes were tested. Each suffix was preceded by 6 pseudo-roots (e.g., amas-erie). One hundred and thirty-four native French speakers were asked to freely complete these 72 pseudo-roots involved in short definitory sentences. Accuracy in suffix production was analyzed as a function of lexical variables (type and token frequency of the French suffixed words) and individual variables (bilingualism and level of education). Data show a wide range of productivity across suffixes, no effect of lexical frequency on accuracy but higher accuracy for participants with higher levels of education and for participants with two or more languages compared to monolingual speakers. The output of this experiment provides (i) an important basis for our research program, (ii) a new protocol to assess suffix productivity, which could be extended to a wider range of suffixes, and (iii) evidence for a bilingual advantage in morphological awareness.

Oxytocinergic modulation of central lateral amygdala network dynamics underlying social buffering of fear

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The neuropeptide oxytocin is a key mediator of fear reduction in the presence of a companion. This is known as social buffering of fear (SBF). We found that oxytocin in the central lateral amygdala (CeL) activates buffer and inhibits fear neurons suggesting that oxytocin alters local network dynamics to induce SBF. Furthermore, oxytocin is necessary for SBF memory, so that SBF remains effective even in the absence of the companion. However, the precise CeL microcircuit underlying SBF is not known. Here we aim to determine how oxytocin brings about SBF and its memory in the CeL network by using transgenic rats expressing CRE in oxytocin receptor (OTR)-expressing cells. We found that the highly specific OTR agonist TGOT indeed excites fluorescently labelled OTR cells by patch clamp electrophysiology, demonstrating the validity of the transgenic rat line. Next, we retrogradely labelled CeL neurons that project to the parabrachial nucleus (PBN) and found that OTR cells in majority do not project to the PBN directly, and may thus contact the PBN indirectly through PBN projectors. Indeed, TGOT had either excitatory or inhibitory effects on PBN projectors, as evidenced by decreased or increased inhibitory postsynaptic currents (IPSCs), respectively. As OTRs are expressed in GABAergic cells, this suggests that OTR cells directly inhibit or indirectly disinhibit PBN projectors. The opposite effects of TGOT on PBN projectors indicate a complex local microcircuitry that may be involved in SBF. Future optogenetic and molecular experiments will test this and also address the role of CeL-PBN connections in SBF.

Simulating a medical expertise: a robust novel stress induction paradigm in chronic pain patients

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Background: Maladaptive stress responses may play a role in chronic widespread pain (CWP) maintenance and deserve further investigations. Yet existing paradigms are not fully relevant for this population. Hence, we developed a new stress task induction: the Social Benefit Stress Test (SBST), adapted from the Trier Social Stress Test. Instead of a job interview, patients face a simulated medical expert involved in social insurances. The study aims at validating this task in CWP patients.

Methods: Forty women with CWP were included. After a 30-min baseline, they had to justify for 5 minutes their inability to work. Following a recovery period, patients were fully debriefed. The psychophysiological stress response was captured using self-reported stress ratings (VAS), salivary cortisol and amylase, and continuous physiological monitoring.

Results: Compared to baseline, the analysis revealed a significant and transient increase in stress VAS during the stress task ($p<0.0001$, $d=8.96$) associated with a peak in salivary delta cortisol ($p<0.026$, $d=3.5$) and delta α-amylase ($p=0.003$, $d=4.3$) concentrations. Stress VAS positively correlated with salivary biomarkers (respectively $rrm(184)=0.321$; $p<0.001$ and $rrm(227)=0.317$; $p<0.001$).

Physiological stress response was reported through HRV during the task with significant increase in heart rate ($p<0.0006$, $d=4.62$), decrease in HF ($p=0.045$, $d=-3.06$), increase in LF ($p<0.0001$, $d=5.42$) and increase in LF/HF ratio ($p=0.007$, $d=3.76$). There was no significant difference in RMSSD.

Conclusions: The SBST is a relevant experimental model of social stress in CWP patients as it induced objectively and subjectively a reproducible moderate stress response. This task will allow to better study the relationship between stress and chronic pain.

EEG source reconstruction validation with simultaneous intracranial EEG in patients with epilepsy

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Purpose: EEG is essential for assessing brain activity in epilepsy patients and identifying seizure-prone regions. Various inverse solutions are used to detect underlying neural activity. We aim to validate these EEG source reconstructed signals by comparing them with the gold standard of simultaneous intracranial EEG (iEEG).

Method: We obtained simultaneous high-density (hd)EEG iEEG recordings of spontaneous activity from 33 patients and bandpass filtered both between 1 45 Hz. Subsequently, we used eLORETA for source reconstruction and a simplified forward model to estimate potentials at the iEEG electrodes' positions, creating virtual iEEG electrodes. We characterized the quality of the virtual iEEG reconstruction by computing the iEEG virtual iEEG correlation matrix, summarizing the point spread function (PSF) of each iEEG across all virtual iEEGs. Furthermore, for each PSF, we computed the peak localization error (PLE) and spatial deviation (SD) and used them as regressors in a generalized linear mixed effects model with patient-specific random intercepts and slopes to examine their relationship with the iEEG virtual iEEG correlation.

Results: Our findings indicate a median iEEG virtual iEEG correlation of 0.07 (range: 0 to 0.72). For reconstruction quality, the medians of PLE and SD were 3.2 cm and 3.9 cm, respectively. We also identified an anti-correlation between the reconstruction and the PLE and SD metrics with regression coefficients of -0.24 ($R2 = 0.46$) and -0.23 ($R2 = 0.35$), respectively ($p < 0.001$).

Conclusion: Our analysis revealed low iEEG virtual iEEG correlations, likely due to localization errors and activity spread. We designed features to characterize reconstruction quality and will use them to compare different inverse solutions and frequency bands.

Longitudinal relationships between cognitive performance and biomarker profiles in asymmetric Parkinson's disease.

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Motor symptom asymmetry in Parkinson's disease has been associated with distinct clinical and biomarker trajectories. However, the impact of this motor asymmetry on the evolution of neuropsychological symptoms and biomarker trajectories has not yet been investigated. Data were extracted from the Parkinson's Progression Marker Initiative and patients were categorized in two groups: patients with predominantly left-sided motor symptoms (n = 214) and patients with predominantly right-sided motor symptoms (n = 241). Generalized estimating equations were performed using cognitive, psychiatric, motor and biomarker data collected from baseline to 3-year follow-up visits from diagnosis. Analyses revealed distinct longitudinal associations for each subgroup. Namely, patients with predominantly right-sided motor symptoms showed reductions over time in alpha-synuclein and phospho-tau levels as well as significant interactions between these biomarkers that were associated with lower scores in global cognition and higher motor symptoms. Interestingly they displayed lower levels of beta-amyloid over time that were associated with higher processing speed scores. In contrast, patients with predominantly left-sided motor symptoms presented higher concentrations over time of beta-amyloid and total-tau that were associated with higher processing speed scores and higher motor symptoms, respectively. Altogether, results point to differential biomarker and clinical profiles according to motor symptom asymmetry while suggesting a greater vulnerability for patients with predominantly right-sided motor symptoms given the significant interactions found between alpha-synuclein and phospho-tau with cognitive and motor outcomes.

Is looking at an immersive 360° hypervideo similar to direct experience: Stress-related psychophysiological activation in simulations with paramedics

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Emergency contexts are emotionally demanding, particularly for trainees. Novice paramedics may experience high stress in emotionally challenging working situations, which they might encounter infrequently during training. Despite the practice-oriented nature of paramedic training within the Swiss Vocational and Professional Education and Training (VPET) system, complex emergency simulations are limited by practical, logistic, and economic constraints. Educational technologies can enhance these simulations during school classes, allowing students to repeatedly engage in scenarios, including dangerous ones, as needed. To enable the use of these scenarios, this study aims to answer the following research question: “Does an immersive 360° hypervideo of an emergency simulation elicit a psychophysiological activation comparable to when the simulation is performed in the real world?”.

To this end, this field study compared the psychophysiological responses of twenty-three in-training paramedics (Mage = 26 years, SDage = 4.9) during two simulations: a direct simulation involving a real-world road rescue and an indirect simulation viewed through an immersive 360° hypervideo. A multi-method approach, using salivary cortisol and self-reported data, was employed to assess the participants' affective responses during both simulations. Adopting a Bayesian approach, we found that the two conditions elicited comparable psychophysiological responses in terms of cortisol levels and self-reported arousal and stress. Both simulations exhibited the same stress-related decreasing pattern over time: higher anticipatory stress levels before the simulation, which progressively decreased, reflecting well-managed emotions.

These findings suggest that 360° hypervideos could be effectively integrated into educational programs focused on high-emotional-impact scenarios, offering a valuable tool for enhancing paramedic training.

Tanycyte-derived extracellular vesicle annexin A1 modulates microglia and neuronal functions to control energy balance.

Dali

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Energy balance requires accurate crosstalk between the periphery and the central nervous system. In the hypothalamus, tanycytes line the third ventricle walls and floor and extend their processes into the brain parenchyma. Thanks to their strategic location, tanycytes integrate peripheral signals about the metabolic state and modulate neuronal function accordingly. However, how tanycytes communicate with neural cells remains largely unknown. Our pilot experiment highlighted Annexin A1 (ANXA1) as a candidate tanycyte signaling molecule modulating neural cell activity and gene expression in response to energy imbalance. We show that ANXA1 is expressed along the third ventricle, mainly by dorsal tanycytes and classical ependymal cells. Tanycyte ANXA1 expression and localization are regulated by energy imbalance. Notably, our in vitro experiments show that ANXA1 colocalizes with the CD9 marker in the presence of glucose, suggesting its secretion through extracellular vesicles. Proteomic analysis on isolated tanycyte-derived extracellular vesicles confirms the presence of ANXA1 in extracellular vesicles, among classical vesicular proteins. Using publicly available single-cell and single-nuclei RNA sequencing data, we sorted microglia and neurons as putative targets of tanycyte ANXA1: tanycyte ANXA1 modulates microglia number and morphology and SF1-expressing neuron activation. These neural modulations impact brown adipose tissue thermogenesis in response to feeding.
Our results put in light a tripartite communication between tanycytes, microglia, and neurons to modulate energy balance.

The role of immersion, graphic detail and habituation on preschoolers when learning from a virtual presentation.

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In a previous study (Dall'Olio et al., 2024), we observed that preschool children had significantly poorer learning outcomes after following a presentation in immersive virtual reality (IVR) with a virtual reality headset than in the less immersive desktop virtual reality (DVR) with a tablet. One possible explanation is that, under certain circumstances, IVR causes too much cognitive load and therefore impairs learning. The two present follow-up studies investigated respectively two aspects that may reduce the cognitive load in IVR - the level of detail of the presentation (high detail/low detail) and the habituation to the medium (habituated/not habituated). In the first study, we investigated the learning outcomes from a presentation of 159 preschool children aged 4 to 6 depending on the level of detail of the presentation and immersion (IVR/DVR). The children performed significantly better in conditions with a low level of detail. No significant impact of immersion was observed, nor was there any significant interaction between level of detail and immersion. In the second study, we investigated the learning outcomes of 72 preschool children, aged 4 to 6, depending on habituation to the medium used during learning and immersion. We found no significant impact of medium habituation, immersion, and no interaction between these two variables. Level of detail, irrespective of medium, appears to be a crucial factor to consider when designing virtual environments for children. The non-significant impact of immersion (IVR/DVR) suggests that future research is needed to understand its role and underlying mechanisms in a learning context.

Navigating Emotions in Immersive Realities: Insights from Continuous Self-Reports and Multimodal Neural and Physiological Measures

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This study ventures into the emerging intersection of affective neuroscience and affective computing by creating the first public database documenting real-time self-reports of emotional experiences in immersive virtual reality (VR) environments, in conjunction with a range of neural and physiological measures. In this way, we aim to deepen our understanding of the temporal dynamics of emotions by using VR to create highly immersive experiences that closely resemble real-world situations. By incorporating both central and peripheral measures, the study aims to capture the complex interplay between subjective emotional experiences and their neural correlates. The focus is on the fluid nature of emotions, with an emphasis on continuous self-reporting to better understand their evolving nature. VR provides a unique and controlled environment for eliciting and studying emotional responses, thereby enhancing the reliability of the data. Key goals include characterizing the neural and physiological correlates of affective experiences in VR, analyzing their temporal dynamics, and investigating the relationship between subjective reports and physiological data. This comprehensive approach promises not only to enrich the scientific understanding of emotions, but also to improve the predictive capabilities of affective computational models. It represents a significant step forward in accurately capturing and interpreting the full range of human emotional experiences in dynamic, naturalistic settings.

The spatiotemporal brain dynamics of perceiving geometrical optical illusions

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Geometrical Optical Illusions (GOIs) are an example of a mismatch between physical input and its corresponding percept. While they are of great interest for studying vision both psychophysically and computationally, there are scant data regarding their neurobiological underpinning. Here, we recorded 128-channel visual evoked potentials (VEPs) as 23 healthy adults viewed 3 GOIs (i.e., Poggendorff, Zolner, and Hering). Recent work from our team suggested that the different physical properties contributing to these GOIs are themselves operating synergistically rather than independently. VEPs to the same physical input were analysed according to the correspondent percept (i.e., aligned/parallel/straight vs. misaligned/titled/curved for Poggendorff, Zolner, and Hering respectively). First, while we observed late-latency effects with stronger Global Field Power (GFP) for lines perceived as misaligned for Poggendorff (i.e., 516-580ms post stimulus) or parallel for Zolner (i.e., 232-248ms), we found early-latency effect with stronger GFP for lines perceived as curved for Hering (i.e., 110-130ms). Second, in Poggendorff and Hering, we observed topographic changes in comparable time periods to those detected in the GFP effects, whereas in Zolner differences were found in different time periods. These findings extend our understanding of GOIs by showing that different perceptual phenomena that are underscored by different GOIs result in temporally and mechanistically distinct effects.

Towards a bio-plausible model of learning in the ventral visual pathway

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Biological networks have inspired artificial neural networks and both are very powerful to solve complex tasks; yet they learn with different, incompatible 'algorithms' or 'synaptic learning rules'. I propose a model of biologically plausible learning in the ventral visual pathway based on a Contrastive, Local And Predictive Plasticity (CLAPP) learning rule.
Synaptic plasticity is driven by lateral and feedback connections to apical dendrites. Natural eye movements alternating between fixations and saccades provide the “predictive” and “contrastive” samples for learning. The learning rule is local in the sense that synapses only use locally available signals without backpropagation of errors. Importantly, our simulations show that a 'developmental' learning scheme improves performance significantly. The developmental learning scheme consists in respecting “critical periods” — very sensitive periods of high plasticity during development of an infant. Since critical periods in V1 are earlier than in higher areas, different cortical areas (which correspond to layers of a deep network) are trained in our model individually one after the other from bottom to top.
Following standards in machine learning, our work evaluates the performance of learning rules on a large image data base as well as an existing hierarchical object model for artificial data. Our results indicate that learning representations in the visual cortical stream from V1, over V2, V4 to IT is possible without BackProp and without image labels with only a minor performance drop compared to the BackProp based methods in machine learning.

Individualizing Cognitive Training through a Multi-Dimensional Learning Progression System

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A growing interest within the field of cognitive training concerns how to best individualize difficulty adjustment to lead to the most improvements. A promising approach, is the Zone of Proximal Development and Empirical Success algorithm (ZPDES) initially proposed by Clément and collaborators (2015). This technique mostly applied so far to educational software selects the problems to be proposed to the learners based on their learning progression. Here we ask how the ZPDES may compare to more common adaptive staircase in the context of a cognitive task such as the Multiple Object Tracking (MOT). As participants track with their attention moving dots, task difficulty can be adjusted based on several different dimensions: number of dots to track, speed of the dots, tracking duration, spacing between dots and time to respond. At the start of the training, a set of pre-defined low-difficulty levels among the several dimensions possible is randomly presented to the participant to evaluate i) the success rate and ii) the learning progress in each dimension. The ZPDES then defines the space of activities to be presented to the participant, balancing between exploring new dimensions and selecting difficulties that maximize their learning. To assess the efficiency of the ZPDES we will present preliminary data collected during a previous study by Adolphe and collaborators that compared a group training with interleaved adaptive staircases sampling the different MOT dimensions listed above and a group training with the same MOT task but using the ZPDES.

Neuronal autophagic cell death in neonatal hypoxia-ischemia: involvement and molecular mechanisms

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We previously provided evidence that autophagy (physiological process of degradation and recycling of dysfunctional organelles and proteins) could be overactivated and involved in neuronal death in rodent models of perinatal cerebral hypoxia-ischemia (HI). We also reported the presence of autosis, a Na+/K+ ATPase alpha-subunit (ATP1a)-dependent type of autophagic cell death, in dying CA3 neurons of the hippocampus following perinatal cerebral HI. However, the relevance and molecular mechanisms of neuronal autosis have never been investigated. We showed the occurrence of neuronal autosis in primary cortical neurons using two different stimulations enhancing autophagy flux and neuronal death: a neurotoxic concentration of Tat-BECN1 (autophagy-inducing peptide) and a hypoxic/excitotoxic stimulus (mimicking neuronal death induced by cerebral HI). Both stimulations induce autophagic neuronal death (dependent on canonical autophagic genes and independent on apoptotic, necroptotic or ferroptotic pathways) with all morphological and biochemical (ATP1a3-dependent) features of autosis. Autosis is associated with an increase in ATP1a3-BECN1 interaction (prevented by cardiac glycosides treatment) suggesting that this interaction plays an important role in neuronal death in HI conditions. We also showed that despite preventing autophagosome formation is protective, inhibiting the degradative step of autophagy did not provide neuroprotection. In order to evaluate whether selective forms of autophagy could be involved in neuronal autosis, we analyzed: the overall effect of autosis on organelles content and flux, and the proteomic profiling of autophagosomes' content in HI conditions. We found that key organelles (mitochondria and Golgi apparatus) are selectively affected. Our results suggest that autosis plays major role in hypoxic-ischemic neuronal death and that elucidating the molecular mechanisms of neuronal autosis could lead to new neuroprotective strategies for the treatment of perinatal hypoxic-ischemic brain damage.

Apparent Diffusion Coefficient fMRI shines a new light on white matter resting-state connectivity, as compared to BOLD

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Resting-state functional MRI (rs-fMRI) detects spontaneous low-frequency oscillations in the MRI signal at rest. When occurring simultaneously in distant brain regions, they define functional connectivity (FC) between these regions. While blood oxygen level-dependent (BOLD) fMRI serves as the most widely used contrast for rs-fMRI, its reliance on neurovascular coupling poses challenges in accurately reflecting neuronal activity, resulting in limited spatial and temporal specificity and reduced sensitivity in white matter regions. To overcome these limitations, apparent diffusion coefficient fMRI (ADC-fMRI) is emerging as a promising alternative. This approach captures neuronal activity by monitoring changes in ADC resulting from activity-driven neuromorphological alterations such as transient cell swelling. Using graph theory on resting-state FC networks, this study confirms that ADC-fMRI mirrors the positive correlations observed in BOLD-fMRI in gray-to-gray matter edges (GM-GM), while diverging significantly from BOLD-fMRI for white-to-white matter (WM-WM) connections. While comparable average clustering and average node strength were found for GM-GM connections, higher average clustering ($p < 10\text{-}3$) and average node strength ($p < 10\text{-}3$) for ADC-fMRI in WM-WM edges suggests that it captures different information to BOLD in the WM. In addition, a significantly higher FC similarity between subjects for ADC-fMRI (mean 0.70, 95% CI [0.68, 0.72]) than BOLD-fMRI (0.38 [0.31, 0.44]) in WM-WM connections suggests a higher reliability of ADC-fMRI in this brain tissue, demonstrating its broader applicability across the entire brain and reduced sensitivity to physiological noise. These results indicate a higher sensitivity and robustness of ADC-fMRI in the WM, and encourage its use to further investigate WM FC.

Interictal structure-function coupling revealed by connectome spectrum analyses and its relationship to surgical outcome.

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Abstract: Epilepsy is associated with altered brain network organisation. This work uses graph signal processing to study brain structure-function coupling, interpreted as integration-segregation balance, during interictal epileptic discharges (IEDs) to predict surgical outcomes. IEDs of 31 temporal lobe epilepsy patients were extracted from hd-EEG recordings and projected in the source space. Source activities were then summarised into 118 regions of interest (ROI) through single value decomposition (SVD). Using a consensus structural connectome (SC), the ROI time-series were decomposed as the sum of the SC graph Laplacian eigenvectors, termed 'network harmonics'. The energy spectrum of the transformed signal was divided into low-frequency harmonics (LF, reflecting network integration) and high-frequency ones (HF, reflecting segregation). The LF components were used to reconstruct the part of the signal mostly coupled to the underlying structure, while the HF components were used to reconstruct the decoupled one. The norms of the coupled and decoupled signals were calculated over all brain regions and the dynamics of their energy distribution along the IED were compared with a cluster-based permutation test. The integration, i.e. the LF harmonics contribution, at the IED's peak was examined between seizure-free and non-seizure-free patients. Results showed increased integration during IEDs compared to baseline ($p<0.05$) and suggest lower integration in non-seizure-free patients, though this last finding was not statistically significant ($p=0.08$). Next steps will address methodological issues such as SVD sign ambiguity and EEG leakage in source reconstruction, as well as increase the sample size, to assess the validity of this metric as surgical outcome predictor.

Myelin alterations in the skin from synucleinopathies

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Myelin is the lipidic membrane that wraps around axons, allowing rapid saltatory conduction of action potentials. Loss of myelin in the central nervous system plays a role in neurodegenerative diseases, but little is known about how the peripheral nervous system is affected.

In this study, we ultrastructurally characterize myelin sheaths in human dermal nerve fiber bundles among post-mortem donors diseased with synucleinopathies (Parkinson's Disease - PD, Dementia with Lewy Bodies - DLB, Multiple System Atrophy - MSA) and non-neurological controls, by using correlative light and electron microscopy (CLEM) and ELISA, to quantify levels of myelin proteins responsible for myelin compaction.

We report a significant difference in the load of myelin damage in our cohort, with PD and DLB showing a significant higher myelin damage compared to non-neurological control and MSA groups. We defined a total myelin damage score that can be used as a disease classifier, showing high sensitivity, specificity, accuracy and area under the curve (AUC).

In addition, we didn't find any significant correlation between myelin damage and age, post-mortem delay and fixation time, showing that, in our cohort, the differences in myelin damage in the donor groups are not a direct effect of any of these individually, nor their linear combination.

Taken all together, our results may suggest a different involvement of the peripheral innervation in the synucleinopathies and non-neurological controls. The discovery of an additional biomarker that is effective in diagnosing and differentiating between the synucleinopathies would have significant implications for early detection, disease monitoring and treatment.

Unveiling an endogenous source of cholinergic transmission in the Habenular complex

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The neural circuits of the epithalamic Habenular complex (Hb), composed of the lateral (LHb) and medial (MHb) subdivisions, are associated with coding information originating from external cues with both negative and positive valence. While LHb and MHb afferent/efferent connectivities differ, both of their projection patterns suggest a contribution to hedonic homeostasis via control of serotoninergic and dopaminergic neuromodulation. Indeed, both subnuclei appear to function as relays between the forebrain with midbrain monoaminergic nuclei. Signaling within the Hb is predominately glutamatergic, GABAergic and cholinergic. In contrast to the physiological properties of glutamatergic and GABAergic afferent inputs to the Hb, the source and functions of endogenous cholinergic afferent inputs to the Hb remain, for the most part, to be determined. I have identified a cholinergic plexus in the Hb originating from the basal forebrain (BF). Using immunohistochemistry, optogenetics and ex vivo electrophysiology, my results show that BF axons co-transmit acetylcholine and glutamate onto neurons located in the ventro-lateral portion of the LHb, eliciting fast inward excitatory post-synaptic currents mediated by glutamatergic AMPA receptors and slow outward currents produced by cholinergic muscarinic receptor activation. We also show that, in cell-attached recordings, this mixed glutamatergic/cholinergic transmission has heterogeneous effects on cellular firing, thus suggesting a high degree of diversity in the system. Until present no convincing evidence had been given on the fact that cholinergic synaptic inputs to the Hb existed and were functional. In this sense, our results represent a novelty with potentially important implications for habenular physiology.

Modulation of Emotional Memory

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Over the last decade, basic research in animals and humans has shown that after a memory is formed, it can become malleable again and open to modification through a process termed reconsolidation (Elsey, Van Ast, & Kindt 2018). Memory content can be updated with a behavioral intervention after reactivation of the established memory (Hupbach et al. 2007, 2008). One behavioral intervention that has been used in the lab to influence reconsolidation of emotional memories is Tetris gameplay applied after reactivating the memory of an emotional film. This intervention showed a decrease in intrusive memories of an emotional film over time (Hagenaars et al. 2017; James et al. 2015; Kessler et al. 2020). To date, it is unclear how such behavioral interventions during memory reconsolidation may alter the characteristics of the memory content, context, the physiological arousal of the memory, and the subjective feeling of the memory. In our study, we recruited 138 healthy adult participants and allocated them to four groups: 1) a reactivation + Tetris group (R+I+), 2) a reactivation + no-task group (R+I-), 3) a no-reactivation + Tetris group (R-I+), and 4) a no reactivation + no Tetris group (R-I-). Our primary aim was to replicate previous studies showing a reduction in intrusive memories in the R+I+ group, then exploring how the intervention affected other memory characteristics. We indeed found a reactivation*Tetris interaction, where the group that received both had a bigger change in intrusive memories of the film than the group that received a reactivation only (R+I-).

Maternal fiber to fetus: Exploring the role of gut-derived short chain fatty acids in neural development and metabolism

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The rising prevalence of obesity and type 2 diabetes necessitates innovative approaches to address metabolic dysfunction. Western dietary habits, characterized by high fat, sugar, and low fiber, disrupt the gut microbiome, impairing vital gut-brain signaling pathways and exacerbating metabolic imbalances.

Although the gut microbiota's role in metabolism is acknowledged, the precise molecular mechanisms remain elusive. Fermentation of dietary fiber produces short-chain fatty acids (SCFAs), namely acetate, propionate, and butyrate, exhibit promising effects on glucose regulation and mood modulation via the gut-brain axis. However, the specific involvement of SCFAs and free fatty acid receptors (FFARs), in metabolic regulation requires further elucidation.

Recent research has highlighted the pivotal role of maternal gut microbiota in offspring metabolic resilience where maternal propionate production emerges as a critical determinant shaping embryonic metabolic and neural systems, influencing glucose homeostasis and energy balance during post-natal development and through adulthood. (ref) Offspring lacking maternal gut microbiota, and in term, short chain fatty acids, display heightened susceptibility to metabolic disturbances and autonomic dysregulation, a phenomenon observed in FFAR3 knockout offspring despite maternal high fiber intake. Based on these findings, we hypothesize that maternal gut-derived SCFAs and neuronal FFAR3 mediate these effects.

Here, unravel mechanisms underlying SCFA and FFAR-mediated protection against neuro-developmental and metabolic dysfunction by manipulating maternal diet during pregnancy and evaluating expression profiles of FFAR3 and downstream targets. Using cre-lox mouse models, we identify neuron-specific roles of FFAR3 in the protective mechanisms of SCFAs and their long-lasting effects. These efforts aim to identify novel therapeutic targets by manipulating maternal nutrition to prevent offspring metabolic disease.

Neural Representation of Appraisals

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Appraisal theory of emotions posits that emotions are triggered by appraisals i.e. automatic cognitive evaluations of stimuli. Each emotion is thought to be caused by a specific appraisal pattern. However, researchers often disagree as to the exact content of the appraisal process and recent studies questioned the importance of appraisals over categorial emotion approaches (see Horikawa et al., 2020). Here, we strive to identify the brain activation patterns of appraisals taken from the Component Process Model of Scherer (2001, also see Sander et al., 2005) and to demonstrate that the right appraisal selection is key when testing appraisal vs categorical theories. In our study, 95 video clips taken from general-public movies were shown to 104 healthy adults in a passive viewing task in fMRI. In an independent sample of 30 people, we collected online 20 appraisal self-reports and 13 emotion self-reports on the same videos. We present in our poster the activation maps for each of the appraisals. Future analysis will focus on the categorical vs dimentional emotion debate.

Functional network centrality indicates interactions between APOE4 and aging across the clinical spectrum of AD.

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*** The data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp- content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf*

Advanced age is the most important risk factor for Alzheimer's disease (AD), and carrier-status of the Apolipoprotein E4 (APOE4) allele is the strongest known genetic risk factor. Many studies have consistently shown a link between APOE4 and synaptic dysfunction, possibly reflecting pathologically accelerated biological aging in persons at risk for AD.
To test the hypothesis that distinct functional connectivity patterns may be used to characterize APOE4 carriers across the clinical spectrum of AD, we investigated 128 resting state functional Magnetic Resonance Imaging datasets from the Alzheimer's Disease Neuroimaging Initiative database, representing all disease stages from cognitive normal to clinical dementia. Brain region centralities within functional networks, computed as eigenvector centrality, were tested for multivariate associations with chronological age, APOE4 carrier status and clinical stage (as well as their interactions) by partial least square analysis (PLSC).
By PLSC analysis two distinct brain activity patterns could be identified, which reflected interactive effects of age, APOE4 and clinical disease stage. A first component including sensorimotor regions and parietal regions correlated with age and AD clinical stage ($p<0.001$). A second component focused on medial-frontal regions and was specifically related to the interaction between age and APOE4 ($p=0.032$).
Our findings are consistent with earlier reports on altered network connectivity in APOE4 carriers. Results of our study highlight promise of graph theory-based network centrality to identify brain connectivity linked to genetic risk, clinical stage and age. Our data suggest the existence of brain network activity patterns that characterize APOE4 carriers across the clinical spectrum of AD.

Functional Language Mapping with Stereo-EEG

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In epilepsy surgery, functional mapping plays a key role in individualizing cortical resections and limiting their potential negative consequences on language functions. Despite the growing popularity of stereo-EEG, functional language mapping with stereo-EEG electrodes is not a standardized procedure. Here, we systematically assessed cortical responses to simple language tasks in patients undergoing stereo-EEG monitoring.

Three basic tasks were used to examine language-related cortical activity: picture naming, auditory naming and sentence completion. 7 patients participated in the study at Geneva University Hospitals' Epilepsy Monitoring Unit. Preprocessing included applying a high-pass filter at 1Hz, a line noise comb notch filter, and rejecting epochs with significant artifacts caused by line noise. For each presentation modality, baseline-normalized, event related spectral perturbation (ERSP) and event-related potentials (ERPs) were computed. These measures were time-locked to the delivery of the stimulus and time-warped to account for varying stimulus durations (for the auditory naming task) and realign response events. A significance threshold of 95% was applied to each frequency in comparison to the baseline.

The ERP and ERSP preliminary analysis on X 7 participants revealed significant functional response of 62, 38, 40 channels on average respectively for visual naming, auditory naming, and sentence completion. We describe 4 typical response patterns: stimulus/response evoked ERPs and ultra-HF (150-300 Hz) power drop, broadband frequency (300 Hz) power increase with decay towards end of stimulus presentation, HF (50-150 Hz) power increase and LF (<20 Hz) power drop during stimulus presentation, and anticipatory HF power increase. Presence of these distinct patterns suggest the involvement of multi-level processing.

Our functional mapping protocol assesses language function through visual and auditory inputs and elicits robust cortical activity in on average 7.5 % of channels per patient (64 channels out of 851 channels total). Further work will probe the correspondence between stereo-EEG, fMRI and direct electrical stimulation-based language mapping and establish the clinical relevance of the various response patterns.

Impaired β-adrenergic vasodilator function in hypertensive patients with symptoms of depression.

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Introduction: Hypertension and depression are amongst the most common chronic physical and mental conditions worldwide. The two conditions cluster, however the mechanisms underlying the association are not well understood. Hypertension complicated by affective disorders may be characterised by high sympathetic activity. We investigated whether symptoms of depression may be associated with impaired endothelium-dependent β2-adrenergic vasodilator responses.

Methods: Hypertensive subjects with no previous history of diabetes or cardiovascular disease were recruited from the hypertension outpatient service at St. Thomas' Hospital, London. Detailed medical history and baseline characteristics including blood pressure (BP), heart rate (HR), routine biochemistry including C-reactive protein (CRP) and low-density lipoprotein (LDL) were obtained during a single study visit. Plasma concentrations of normetadrenaline were measured as a marker of resting sympathetic activity. Depression symptom severity was assessed using the Patient Health Questionnaire-9 (PHQ-9). The pulse wave response to the β2-adrenergic vasodilator salbutamol (PWRS) was assessed using radial tonometry to measure the change in augmentation index after inhalation of 200μg salbutamol from a metered dose inhaler with spacer device.

Results: 100 subjects (62% male, mean ± SD age 41.0±11.6 years) were recruited. 79% were on pharmacological treatment for hypertension. Mean PHQ-9 depression score was 8.8±6.2, consistent with a high prevalence of depression. After adjusting for confounders (age, sex, smoking status, body mass index, BP, HR, CRP, LDL, treatment for hypertension), PWRS was significantly related to depression score (β= 0.447, P=0.002). Depression score was also significantly associated with plasma concentrations of normetadrenaline (β= 0.605, P<0.001) and after adjusting for plasma normetadrenaline level, the association between PWRS and depression score was no longer significant (β= 0.343, P=0.102).

Conclusions: These results suggest that in hypertensive subjects with depression, an impaired endothelium-dependent β2-adrenergic vasodilator response is mediated by a high level of sympathetic activity which could contribute to cardiovascular complications.

The Fleeting: a novel age-dependent mouse ultrasonic vocalization

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Mouse ultrasonic vocalizations (USVs) represent a major mode of communication, mostly during infancy, with the main goal of eliciting retrieval and maternal care by the dam. The study of USVs and their spectral features (temporal and frequency profiles, waveform, duration, or vocalization rate) has been growing over the past decade. Literature has shown that USVs are important carriers of relevant information such as emotional state, social hierarchy, territorial boundaries, and mating behaviour of rodents. Importantly, factors such as environment, mouse strain, genetic background and developmental stage, influence the spectral characteristics of the USVs, thus underscoring the need for detailed characterization of the USV repertoire across different paradigms.

While studying the vocal repertoire of C57BL/6 mice during infancy, we found a novel, previously unreported vocalization, which we describe in this study. Here, using the deep learning-based algorithm of DeepSqueak software, we detected neonatal USVs from recordings of 24 male and 27 female C57BL/6 mice and manually identified the novel vocalization across all collected spectrograms. The novel vocalization consisted of two acoustic elements separated by a narrow silent interval and, strikingly, was only present in the mouse vocal repertoire until the second postnatal week. To reflect its transient nature, which is not characteristic of any of the other already described mouse USVs, we named it “Fleeting”. Our work encompasses a comprehensive analysis of the time-frequency contours of the Fleeting, and explores age-dependent and sex-dependent aspects of its spectral features.

Our results bring to light a new development-dependent player in the already complex mouse vocal repertoire, offering insight into the maturation of their communication system. The Fleeting holds promise as a potential developmental biomarker for future investigations on neonatal behaviour and development.

Longitudinal Analysis of Brain Function-Structure Dependencies in 22q11.2DS and Psychotic Symptoms

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BACKGROUND: Understanding how brain function and structure relate to one another, compared to conventional unimodal analysis, opens a new biologically-relevant assessment of neural mechanisms. However, how function-structure dependencies evolve throughout typical and abnormal neurodevelopment remains elusive. The 22q11.2 deletion syndrome (22q11.2DS) offers an important opportunity to study the development of function-structure dependencies and their specific association to the pathophysiology of psychosis.
METHODS: Previously, we used graph signal processing to combine brain activity and structural connectivity measures in adults, quantifying functional-structural dependency (FSD). Here, we combined FSD with longitudinal multivariate partial least squares correlation (PLS-C) to evaluate FSD alterations across groups and among patients with and without mild to moderate positive psychotic symptoms (PPS). We assessed 391 longitudinally repeated resting-state functional and diffusion-weighted magnetic resonance imaging from 194 healthy controls and 197 deletion carriers (age span 7-34, data collected over a span of 12 years)
RESULTS: Relative to controls, patients with 22q11.2DS showed a persistent developmental offset from childhood, with regions of hyper- and hypo-coupling across the brain. Additionally, a second deviating developmental pattern showed an exacerbation during adolescence, presenting hypo-coupling in frontal and cingulate cortex and hyper-coupling in temporal regions for patients with 22q11.2DS. Interestingly, the observed aggravation during adolescence was strongly driven by the PPS+ group.
CONCLUSIONS: These results confirm a central role of altered FSD-maturation in the emergence of psychotic symptoms in 22q11.2DS during adolescence. The FSD deviations precede the onset of psychotic episodes and thus offer a potential early indication for behavioral interventions in individuals at risk.

Learning to control the visual cortex and affecting visual attention via fMRI-based Neurofeedback

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Attention emerges from top-down regulation involving bilateral fronto-parietal networks that interact with early visual areas. Following frontal or parietal brain lesions and therefore disruption in such system, unilateral spatial neglect (USN) may emerge: a syndrome denoted by impaired awareness of stimuli present in the visual field despite absence of pure sensorial loss. Neuromodulation via functional MRI (fMRI) based real-time neurofeedback (NFB) of early visual areas has accounted for partial restoration from this condition. However, specific mechanisms underlying successful modulation of visual areas via fMRI NFB are still unclear. For this reason, we couple the spatial precision of fMRI with the temporal resolution of EEG in EEG-MRI multimodal imaging fashion during fMRI NFB training to unravel structural and functional correlates of such learning process in the brain. Results from this study will further help to develop an informed EEG based NFB based protocol to apply in clinical context for USN rehabilitation. We recruited 60 healthy participants (30 experimental and 30 control) and trained them in regulating the inter-hemispheric balance between left and right visual cortex over the course of 2 NFB sessions. At the same time, we collected several neural and behavioral measures before and following NFB training as well as EEG recording during the second session of NFB. Participants were able to learn how to control the balance between left and right visual cortex according to the imposed training direction and this affected visual attention. We related this learning process to the involvement of different brain rhythms and neural signatures, including higher level brain networks activation. Our results further confirm the efficacy of fMRI NFB as a valid neuromodulation tool as well as a promising alternative in the treatment of visual attention-related deficits. At the same time, they offer further insights on the neural mechanisms allowing NFB success.

Eyes Wide Shut: The Impact of Eye Visibility on Facial Emotional Recognition

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The ability to interpret emotional facial expressions is a central emotional skill in social cognition. In Western cultures, the eyes are one of the central sources of information for perceiving these expressions. However, the inability to perceive the eyes can lead to different interpretations; eyes obscured (e.g., by dark glasses) may see, whereas closed eyes surely cannot; but in both cases, they are inaccessible to our perception. Thus, do we interpret facial expressions similarly, independently of the eyes' accessibility ? Or is our appraisal dependent on how we represent what the others can see? To investigate this question, we exposed 50 participants to images of emotional faces (anger, fear, happiness) and neutral expressions with open, closed, or obscured eyes (by dark glasses), and asked them to report on discrete emotion scales the facial expressions they perceive. Overall, participants identified the expected emotions, but the patterns of recognition for the eyes condition differed. Anger and fear expressions were recognised better when eyes were open, then behind glasses, and finally with closed eyes. Happiness on the other hand was not different through conditions. Based on previous literature, we know that the eyes area is central for anger and fear recognition, while it is not for happiness, explaining the results. Next steps will however focus on the divergence between closed eyes and hidden-by-glasses eyes, to understand why this difference occur.

Intra-Uterine Position Shapes Anxiety Trait and Neurogenesis from Childhood to Adulthood.

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C57BL/6J mice, despite genetic and housing uniformity, exhibit interindividual differences in trait anxiety, inversely linked to adult hippocampal neurogenesis. We hypothesize that subtle hormonal variations during gestation may influence interindividual differences in anxiety and neurogenesis.

To do so, we performed a caesarean section on pregnant females at gestational day 18.5, allowing us to precisely identify the position and gender of the foetuses. In a cross-sectional study, we collected the brains and blood to analyse the effects of intrauterine position (IUP) on hormone levels, brain anatomy, and neurogenesis in the hippocampus. In a longitudinal study, we fostered the foetuses according to their IUP and we assessed trait anxiety at weaning and in adulthood.

Our findings indicate that IUP significantly influences steroid levels in the pup's blood and brain, leading to differences in adult neurogenesis. Females surrounded by two male foetuses (2M) exhibit higher steroid levels and increased neurogenesis compared to females surrounded by no males (0M). Both male and female 2M mice display higher anxiety levels at P22 and P56.

Further, 2M female foetuses show increased cell proliferation and immature neuron formation, whereas males in these groups exhibit reduced neurogenesis. Hormonal analysis reveals that 2M female foetuses have decreased corticosterone and progesterone levels in serum and brain, while 2M male foetuses show increased progesterone and testosterone levels.

Our study underscores the significant impact of intrauterine position on brain plasticity and anxiety traits, emphasizing the role of inter-individual differences in the hormonal environment in utero in shaping these traits.

Constant “baseline” electrical stimulation can improve vestibular function in patients implanted with vestibulo-cochlear implants

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Introduction: Prototypes of vestibular implants are under development to rehabilitate patients with bilateral vestibulopathy (BV), mimicking the physiology of the vestibular system. While waiting for a take-home version, an alternative and simplified approach consists in delivering constant electrical stimulation to restore a “baseline” activity in the vestibular system. This study aimed to quantify the benefits of such a “baseline” stimulation (BS) delivered to semicircular canal afferents during prolonged periods of activation.

Methods: Three patients with BV received a modified cochlear implant providing extra-cochlear electrodes implanted in the semicircular canals. The patients’ speech processor was programmed to deliver a BS to the posterior semicircular canal for a period of 2.5 months. Objective and subjective measurements (gait analyses, dynamic visual acuity, posturography, questionnaires) were acquired throughout the stimulation period and afterwards over 6 sessions.

Results: For patient-1, DHI questionnaire scores improved from 52 to 30 throughout the BS, reflecting clinically relevant changes. After BS deactivation, DHI score increased to 48, representing a decline of functional status. The number of steps in the tandem walk task increased from 2 to 10 steps. Results for patient-2 and patient-3 do not present any changes at this step of analysis.

Discussion: Results in at least one patient demonstrate that vestibular deficits were reduced during the BS, complemented by positive patient feedback: “the implant allows me to walk in a straight line”. Objective and subjective gains disappeared when BS was deactivated. While this stimulation shows promise, its effectiveness may vary among patients, highlighting the need for devices that employ stimulation methods closer to human physiology.

Rhythmic priming of syntactic processing: does semantics play role?

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Accumulating evidence shows improved syntactic processing following exposure to a rhythmically regular compared to an irregular musical prime, environmental noise, or silence. One potentially shared system between musical rhythm and language processing may be responsible for the construction of hierarchical sequences. Following findings of a shorter-lived rhythmic priming effect in Jabberwocky and more precise neural tracking of linguistic constituents in natural language than in Jabberwocky, we hypothesised that a) hierarchical structure building constitutes a key shared mechanism between rhythm and language processing and b) semantic information may also play a role in structure building.

We predicted a longer priming effect than the reduced effect over three sentences reported for Jabberwocky. We also expected positive relationships between tasks measuring structural processing in language and rhythm. French-speaking typical adults listened to 32-second rhythmic primes before completing six-sentence blocks of grammaticality judgement. Surprisingly, results showed a reduced priming effect present only in the first sentence after a prime. Unsurprisingly, overall grammaticality judgement d' correlated with performance in a rhythm discrimination task.

These data showcase that the rhythmic priming effect is reduced when typical speakers process sentences containing linguistic information available at all levels compared to atypical populations processing natural language or typical adults processing syntactic structures in the absence of lexical semantics.

Towards the development of a neurocomputational profile of peruvian women with symptoms of Complex Post Traumatic Stress Disorder

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In 2022, more than seventeen thousand cases of violence against women were perpetrated in Perú (MINSA, 2022). The repetition of traumatic events can generate self-concept problems and affective dysregulation, turning into a more pervasive clinical condition: Complex PTSD (CPTSD) (Jowett et al., 2020). Nevertheless, the specific neural, cognitive and affective characteristics of CPTSD in women are unclear. Following the RDoC framework for psychopathology research (Kozac & Cuthbert, 2016), we aim at contributing to the development of a neurocomputational profile of women with CPTSD using behavioral, electrophysiological and self-report measurements.

To achieve this, we will recruit 134 women between 18 and 55 years old with PTSD or CPTSD symptomatology assessed by the International Trauma Questionnaire (ITQ) and the Frequency of Traumatic Events Scale (LEC), and 100 healthy controls. Three behavioral tasks will be examined: a two-bandit task computationally modelled with Reinforcement Learning algorithms, an Auditory Oddball Task to evaluate neural Event-Related Potentials (ERP) and a 3D Body Image Scale. Furthermore, we will explore the relationships of Sexual Subjectivity, Emotional Dysregulation, Hallucinations, Body Awareness and Eating Disorder Symptomatology with CPTSD symptomatology and the behavioral tasks results.

We expect to contribute empirically and theoretically to the evaluation and prediction of treatment response in women who suffered violence. Particularly, we expect to contribute to the establishment of boundaries of CPTSD with other diagnoses, the identification of CPTSD subtypes and the development of treatment strategies. This is critical to improve the well-being of women who suffered violence and diminish the economic impact of violence against women in society.

The predictive value of neurological factors for differentiated attention functions in children and adolescents with the genetic disorder neurofibromatosis type 1

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Neurofibromatosis type 1 (NF1) is one of the most prevalent rare genetic diseases, confronting patients with numerous medical (neurological, cutaneous, osseous) and neuropsychological symptoms. To identify risk factors and allow for targeted neuropsychological intervention, potential associations between the heterogenous somatic and cognitive phenotype have been proposed.
The present study harnesses the benefits of machine learning analysis to investigate potential non-linear associations between the medical and neuropsychological profiles of n=236 pediatric NF1 patients. A total of 14 models was constructed to predict objective, behavioral, and parent-rated measures of 7 distinct attention domains based on medical characteristics (eg. CNS tumors, focal MRI signal intensity).
While the young patients' attention scores differed significantly from the expected, normative values, only behaviorally observed measures of sustained attention, hyperactivity and observed attention problems could be predicted from the chosen biological factors. Additional information on the location of neurological alterations did not significantly improve the predictions. The most important predictors were younger age and male sex, with significant age-sex interactions in sustained attention and overall observed attention deficits.
These findings highlight the relevance of attention deficits in pediatric NF1 patients, especially in young boys and adolescent girls. However, the results indicate the absence rather than the non-linearity of associations between gross NF1-related neurological characteristics and attention skills. Therefore, it is recommended to prioritize age and sex over neurological characteristics as risk factors when planning neuropsychological interventions to prevent psychosocial consequences of attention deficits on the quality of life of young patients with NF1.

Keywords: neurofibromatosis type 1, attention, predictive machine learning analysis, neuropsychology, focal areas of signal intensity

Auditory closed-loop modulation of slow wave sleep to treat major depressive disorder

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Background: Major depressive disorder (MDD) is a leading cause of reduced quality of life worldwide. This study investigates the fast-acting antidepressant effects of slow wave sleep (SWS) suppression in individuals with MDD, focusing on sleep physiology and non-invasive markers of homeostatic and associative plasticity.

Methods: The study will assess the effects of SWS suppression in MDD patients (N=30) and healthy controls (N=30) using a within-subject design over four sleep laboratory nights (adaptation, baseline, and two experimental) and a follow-up after one week. During experimental nights, SWS will be automatically detected and suppressed through closed-loop auditory stimulation, with a sham night in a counterbalanced order. High-density EEG will measure sleep physiology, while neuroplasticity effects (via TMS, tDCS, and EEG) and cognitive and clinical outcomes will be assessed post-baseline, post-experimental nights, and at follow-up.

Results: We anticipate selective suppression of SWS based on previous findings in healthy participants. Our primary hypothesis is that SWS suppression will significantly reduce depressive symptoms in MDD participants. Additionally, we aim to demonstrate a differential effect of SWS suppression in MDD patients compared to healthy controls, potentially achieving a more 'optimal' neuroplasticity window.

Conclusion: If confirmed, this study could pave the way for a new fast-acting sleep-based treatment for MDD, significantly improving patients' quality of life.

Incorporating Connectome Information to EEG Source Reconstruction - Validation Experiment

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Source reconstruction is a method used to infer brain activity from external measurements, such as EEG recordings. This technique is particularly valuable in epilepsy, where it helps localize the focal epileptic source, guiding surgical resection of epileptic tissue. However, source reconstruction faces the challenge of the inverse problem, which is inherently ill-posed. Solving this problem requires prior knowledge about the signal to be reconstructed, such as its smoothness or sparsity.

Traditional EEG source reconstruction methods rely on heuristic priors, which are not always optimal. A novel approach leverages recent findings in connectomics, suggesting that brain activity, when represented through graph signal processing of connectomes, exhibits a sparse graph Fourier transform. By imposing this sparsity constraint on the reconstructed signal, the new technique aims to improve localization accuracy.

To validate this technique, we conducted an experiment using a dataset comprising 30 epilepsy patients who were cured following surgical intervention. We performed source reconstruction on pre-surgical EEG recordings to estimate the epileptic tissue location. These estimations were then compared to the actual resected regions identified post-surgery. The results demonstrate the potential of connectome-informed priors to enhance the accuracy of EEG/MEG source reconstruction.

Using Augmented Reality to Assess the Usefulness of Retinal Implants in a Naturalistic Environment

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Retinal implants have been shown to provide artificial visual percept to blind people in clinical trials. However, due to technical limitations, existing implants failed to provide a vision that proved useful in a blind patient's every-day life. We have shown that among several implant parameters, the visual angle has the most significant impact on performance, but its minimum required size remains unclear. Here, we aim to determine which visual angle is required for a retinal prosthesis to be useful in daily life.

An augmented reality study was conducted in an artificial street environment. A patient's performance was assessed by exposing normally sighted subjects to a simulation of the POLYRETINA implant where the visual angle varied between 20° (the widest visual angle in current implants), 45° (POLYRETINA's visual angle) and, for control, 110° (full visual angle of one eye). 47 subjects were required to complete the following set of tasks in less than 10 min: post a letter, retrieve money from the ATM and return home. Time taken, task performance, and trajectories were recorded to assess differences in success, dangerous behaviour, and efficiency between the visual angle conditions.

While a visual angle of 45° allows participants to perform more successfully, safely, and efficiently than the 20° visual angle, an even larger visual angle of 110° does not lead to further improvement in most measures. The present combination of simulated prosthetic vision with this naturalistic setup pioneers an approach for the challenge of testing the usefulness of artificial vision in naturalistic scenarios.

Keywords: artificial vision, augmented reality, simulated prosthetic vision, naturalistic setup

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Abstract # 61

The role of lipid droplets during mouse and human brain development

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Neural stem/progenitor cells (NSPCs) form the brain during development and remain active in specific regions during adulthood. A recent publication showed that adult NSPCs contain a large amount of lipid droplets (LDs), intracellular lipid storage organelles, which directly influence NSPC proliferation and metabolism. However, very little is known about the role of LDs in embryonic brain development. We have established a novel endogenous LD reporter mouse line, which allows staining free visualisation of LDs in live and fixed tissues and cells, and showed that LDs are much more abundant in the developing and adult brain than previously thought. We here use this LD reporter mouse to establish an LD brain atlas over a developmental time-course. We show that LD abundance is highly variable, both regionally and temporally. Using genetic and pharmacological means, we will perturb LD usage and numbers and assess the consequences for brain development.
We also utilize human induced pluripotent stem cell- (hiPSCs) derived NSPCs, neural rosettes and cerebral organoids to dissect the role of LDs in human brain development. We show that LDs also vary over cerebral organoid development, and we are currently perturbing their build-up and breakdown to assess their functional role in a human context.

Non-nociceptive neuronal activity is necessary to induce spinal microglial reactivity and chronic pain

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Globally, postoperative chronic pain affects 10-50% of individuals. This neuropathic pain (NP) is a complex pathology with a strong neuroimmune interplay in which microglia has been shown to be a key player. Spinal microglial reactivity has been linked to abnormal peripheral activity coming from primary sensory neurons (i.e. nociceptors and non-nociceptors). Our aim is to further investigate the contribution of nociceptive and non-nociceptive inputs to spinal microglial reactivity in the context of chronic pain.

We first used brief electrical stimulation of the left sciatic nerve of CX3CR1-eGFP mice. This activation of nociceptive and non-nociceptive neurons induced spinal microglial reactivity (proliferation and increase in number of cells, changes in morphology and electrophysiological profile) two days after stimulation. Mice also developed sustained pain lasting up to four days after stimulation. We then used optogenetics to activate the different subpopulations. We activated all sensory neurons (i.e nociceptive and non-nociceptive) using the Advillin-Cre/ChR2-TdTomato line, nociceptors alone using the SNS-Cre/ChR2-TdTomato line and non-nociceptors using a NetrinG1-Cre/ChR2-TdTomato line. Like after the electrical stimulation approach, spinal microglial reactivity and sustained pain were also observed after optogenetic activation of nociceptive and non-nociceptive neurons, but not after activation of nociceptors or non-nociceptors alone. Finally, we were able to prevent spinal microglial reactivity and lasting hypersensitivity by injection of minocycline, a glial inhibitor.

Overall, our data suggest that a combined activity from both populations of sensory neurons triggers a stronger reactivity of spinal microglia and is necessary to produce lasting hypersensitivity. We also demonstrated a causal link between reactive microglia in the spinal cord and the development of sustained pain after activation of all sensory neurons.

Computational Insights into Degeneracy: Unraveling Neural Circuit Dynamics for Robustness

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Degeneracy is ubiquitous across biological systems where structurally different elements can yield a similar outcome. Degeneracy is of particular interest in neuroscience too. On the one hand, degeneracy confers robustness to the nervous system and facilitates evolvability: Different elements provide a backup plan for the system in response to any perturbation or disturbance. On the other, a difficulty in the treatment of some neurological disorders such as chronic pain is explained in light of different elements all of which contribute to the pathological behavior of the system. Under these circumstances, targeting a specific element is ineffective because other elements can compensate for this modulation.

This investigation employs a comprehensive approach, combining mathematical modeling and supervised machine learning models on neural networks and metabolic pathways. The study demonstrates the importance of degenerate solutions for the survival and evolution of underlying networks. Through this computational lens, the research reveals the intricate interplay of degeneracy in physiological contexts, explaining its beneficial role in the robustness of neural circuits. Furthermore, the exploration extends into pathological contexts, revealing intricate details that open novel avenues for therapeutic innovation. By decoding the complexities of degeneracy, this research not only advances our understanding of neural dynamics but also holds promise for the development of more effective therapeutic interventions.

Oxytocin reduces neuroinflammation and protects brain development following pediatric traumatic brain injury

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Traumatic brain injury (TBI) is the leading cause of death in the pediatric stage, with detrimental consequences including psychosocial issues, cognitive deficits and motor abnormalities. In addition to the primary TBI impact, the subsequent neuroinflammatory response can become a contributing and even leading factor to the harmful effect of pediatric TBI on the brain. As such, finding ways to stabilize the reactive microglial phenotype is a key objective for TBI treatment.

One potential factor is the neuropeptide oxytocin. Oxytocin has shown to be neuroprotective in adult neuroinflammatory states, but the mechanisms of effect remain largely unknown, as does its applicability to the pediatric phase. In the current study, we assessed the neuroprotective potential of neuronal oxytocin on microglial reactivity in a mouse model of pediatric TBI.

We subjected P7 B6N male mice to a TBI model of weight-drop impact acceleration injury, which induced a robust inflammatory response in the brain. Treatment with increased oxytocin activity via the Oxt-Hm3Dq DREADD construct reversed the pro-inflammatory effect on microglial density, and cell morphology 24 hours post-TBI. Functional ultrasound assessment showed a disturbance to inter- and interhemispheric brain connectivity in P45 TBI animals, which was partially rescued by the oxytocin treatment. Behavioral assessment showed an impairment to sociability and anxiety in TBI mice, which was reversed by oxytocin treatment. Finally, microglia RNA sequencing revealed putative pathways that can explain the mechanism between oxytocin and its anti-inflammatory effect on microglia.

Our results support that endogenous oxytocin can be a potential protective agent for pediatric TBI by dampening the neuroinflammatory response in microglia and preserving healthy brain development.

Characterisation of upper limb perceptions after stroke

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Alterations in body perception after stroke may affect patient's quality of life and recovery. However, body perceptions are not systematically assessed in clinical routine, probably partly due to a lack of appropriate tools. This leads to a limited understanding of the characteristics of these alterations, their evolution, and their impact on the recovery of other functions (e.g., sensorimotor).
The objective of this study is to characterise disturbances in the perception of the most affected upper limb (aUL) following stroke, by estimating their rate, severity and evolution, their relationship with sensorimotor deficits and recovery, as well as the underlying neural correlates.
We developed a new tool, the Affected Limb Perception Questionnaire (ALPQ), which assesses subjective alterations in the aUL perception (e.g., disownership, illusory movements, perceived temperature, etc.). One hundred sub-acute stroke patients are evaluated after admission to the rehabilitation hospital (T1), at hospital discharge (T2) and at the chronic stage (T3).
While the follow-up is ongoing, we conducted preliminary analyses. At T1, more than 50% of the patients reported at least one altered feeling towards their aUL, regardless of the laterality of the lesion. Moreover, the more severe the motor impairments, the higher the prevalence of the disturbances. However, alterations were reported even with preserved motor function. On the other hand, a substantial portion of patients still suffer from altered perception of their aUL at T2. Further analyses are underway to better understand the profile of patients with such alterations and the relation between their aUL perception and sensorimotor recovery.

Modelling sleep disruption-induced anxiety in mice

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Sleep disruptions are common symptoms in anxiety disorders, which are currently the most common mental illness. Furthermore, lack of sleep increases anxiety in healthy individuals, while good quality sleep is associated with reduced anxiety, indicating that sleep is inherently anxiolytic. Therapies targeted to reverse sleep disruption therefore hold great therapeutic potential. Yet, the underlying mechanisms contributing to sleep disruption-induced anxiety are largely unknown. To shed light on sleep disruption-induced anxiety, we assessed the effects of chronic sleep fragmentation (SF) on anxiety-like behaviour in both female and male mice using the light-dark box and open field tests. In addition, to characterize the effects of SF on sleep architecture, we performed longitudinal EEG/EMG recordings during the SF paradigm. We found that chronic SF, which mainly impacted rapid eye movement (REM) sleep, increased anxiety-like behaviour in female mice, while males were unaffected. Together, our preliminary data support the use of the chronic SF paradigm to investigate mechanisms underlying sleep disruption-induced anxiety in mice and highlight sex-specific effects of SF on anxiety-like behaviour.

Exploration of the association between lateral septum signalling and specific fear and avoidance behaviours towards conditioned social and non-social stimuli.

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Social avoidance is a core feature of numerous disorders. The lateral septum (LS) modulates social avoidance in mice. However, the specific behaviours affected by the LS in this context are not yet characterised. Our aim was to examine the relationship between LS dynamics and specific social approach and avoidance behaviours with high temporal precision using fibre photometry and social fear conditioning (SFC) and to determine if the observed behaviours and associated peaks in signal were social-specific.

C57BL/6 mice underwent surgery to infuse a fluorescent calcium sensor and implant a fibre optic cannula within the LS. Three weeks post-surgery mice were socially isolated for one week, then presented with a series of novel social OR non-social stimuli for 3-min each with a 3-min ITI (SFC-/NSFC-). One week later, mice underwent social or non-social fear conditioning, and were again presented with a series of stimuli during extinction (SFC+/NSFC+). Using fibre photometry and frame-locked video recordings, LS dynamics during exposure to relevant stimuli were correlated with specific behaviours.

LS activity was increased in SFC+ and NSFC+ mice immediately preceding fleeing the stimulus relative to unconditioned mice. However, whilst this response extinguished alongside the extinction of fear in socially fear conditioned mice, mice conditioned to non-social stimuli did not demonstrate the same reduction in LS activity nor an extinction of non-social fear. Furthermore, post-hoc examination of the behaviour of SFC+ mice revealed a subset of extinguishers and non-extinguishers. Extinguishers demonstrated a reduction in LS activity during extinction of social fear whereas non-extinguishers had persistently elevated LS activity similar to those conditioned to non-social stimuli. These results suggest that a reduction in LS activity may be necessary for the extinction of social fear. These findings warrant further investigation, using temporally specific tools, to determine a causal relationship between LS activity and social fear behaviours.

The development of visual engagement and disengagement in autism spectrum disorder

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Introduction: Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by impaired social communication, interaction, and restricted behaviors/interests. A common difference across autistic individuals relies on reciprocal eye contact, notably initiating, sustaining, and modulating gaze; three processes closely related to visual attention. Previous literature has reported difficulties in the visual attention mechanisms of engagement and disengagement in ASD. However, little is known about the developmental perspective of visual (dis-)engagement processes. We aim to examine these processes in preschool and school-aged children with ASD

Methods: To measure (dis-)engagement, we used a gap-overlap eye-tracking task. In the gap condition, the central and peripheral stimuli are separated by a gap. In the overlap condition, the central stimulus remains as the peripheral stimulus appears. The task includes four blocks, comprising 30 trials each of gap and overlap conditions. We calculated the gap effect, which correspond to the difference in saccadic reaction time (SRT) between the overlap and gap conditions (Overlap SRT - Gap SRT). Our cross-sectional sample comprised 87 children, of which 57 children with ASD (age range = 1.8-12.4).

Results: Preschool and school-aged autistic children demonstrate a reduced gap effect, indicating faster disengagement compared to their TD peers. Autistic children spend significantly less time fixating on the central stimulus and spend significantly more time looking at the peripheral stimulus.

Conclusions: Faster disengagement in children with ASD suggests diminished or "fleeting" visual engagement with stimuli. We plan to further investigate the cognitive and autistic profile of these children to understand the implications of diminished visual engagement.

Prestimulus EEG microstates vary with perceptual awareness independently of the cardiac and respiratory phases.

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The perceptual outcome of threshold or multistable stimuli varies with the pre-stimulus global state of the brain, as indexed by EEG microstates. Similarly, awareness also varies with cyclic fluctuations of visceral signals across the cardiac and the respiratory cycle. It remains to be investigated whether the momentary state of the brain contributes to awareness jointly or independently of the bodily phase. We used an orientation discrimination task to determine to what degree the subjective awareness of a visual threshold stimulus varied with the pre-stimulus microstate, cardiac and respiratory phase and whether the brain and body exerted a joint or independent influence on fluctuations of subjective awareness. We compared the pre-stimulus EEG microstates preceding correct aware and unaware trials for the cardiac and respiratory phase. Our findings indicate that the canonical Microstate D was more prevalent in the unaware compared to the aware condition, and the canonical Microstate A accounted more variance during inhalation compared to exhalation. The pre-stimulus activation of Microstate D, which is anticorrelated with attentional networks, preceded trials in which the stimulus was not perceived. Inhalation was instead associated with Microstate A, suggesting increased arousal during this phase. However, we observed no interaction between the bodily phase and awareness, suggesting that the states of the brain and the body exert independent influence on perceptual awareness at the discrimination threshold.

A toolbox of genetically encoded GRAB sensors for multiplex imaging of purinergic transmission

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Purinergic transmitters, such as extracellular ATP, ADP, adenosine and UDP, play essential roles in both peripheral and central nervous systems. With a range of endogenous purinergic transmitters interacting with over ten native receptors, and the possibility of complex conversions among certain neurochemicals, it becomes crucial to develop tools that can monitor them concurrently with high molecular specificity and high spatial-temporal resolution. To achieve this, we developed and optimized a series of GPCR-Activation-Based (GRAB) sensors, which are capable of detecting various purinergic transmitters including ATP, ADP, adenosine and UDP. These sensors show good plasma membrane localizations, high sensitivity, and importantly, high selectivity in distinguishing them from other structurally similar neurochemicals. Novel UDP sensors allowed us to observe increased UDP release e following epileptogenic in vivo. Furthermore, the development and optimization of red-shifted purinergic GRAB sensors made it possible to achieve dual-color imaging of different neurochemicals. Specifically, by combining adenosine and ATP sensor with separated fluorescent spectrums, we were able to simultaneously record their dynamics in culture neurons. Taken together, this expanded purinergic sensor toolbox enabled monitoring of purinergic transmission in vitro and in vivo, unlocking new avenues for comprehending the dynamic and regulation of the purinergic system.

Mapping multiple forms to many meanings: neurocognitive representations of multilingual lexical semantic knowledge.

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UNIGE

Semantic similarity between words varies across languages and cultures, showing higher consistency in closely related languages and differences between monolinguals and multilinguals. Multilinguals convey meaning by choosing from multiple word forms (e.g., chien or Hund for the concept DOG), which is further complicated by lexico-semantic properties, such as polysemy, which do not always correspond cross-linguistically (e.g., the French word lettre which describes both a type of written correspondence as well as an alphabetical unit; while this polysemy is reflected in English, it is not mimicked in German). During language acquisition, these kinds of cross-linguistic discrepancies are referred to as semantic transfer, but few, if any, studies have looked at how cross-linguistic semantic ambiguity is maintained in the multilingual brain after second language (L2) acquisition. In a series of pre-registered and registered studies, we will explore the behavioral and neural mechanisms of multilingualism and semantic ambiguity within and between languages. Behaviorally, we will administer a similarity judgment task in German using word pairs which vary in their French colexification status, examining a group of native French and German multilingual speakers. We will explore the neural underpinnings of ambiguous word processing with and without context in groups of native French speakers and German native L2-French speakers with varying levels of second language experience, focusing on word pairs and sentence-level contexts. Using time-frequency decomposition, we will track spectrotemporal correlates of lexical semantic processing and language experience on a millisecond timescale. We also leverage an exploratory approach to examine how cross-linguistic ambiguity may further modulate L2 ambiguity processing. Our findings will shed light on the interaction between within and between-language ambiguity and its implication in lexico-semantic and processing with and without context.

A new multimodal technique for dissecting dark neurons

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Physiological homeostasis is essential for life as well as brain. Much more energy is consumed to maintain homeostasis than we think. A vast of neurons that cost a quantity of energy but generate few activities in almost every brain area are called dark neurons. Since their functions are hard to be described as they are silent but energy-consumed, we have to define it from different perspectives to reveal their functions accurately. Besides, we need to manipulate their neural activity to study their function. Herein, we intend to develop a multimodal technique composed of functional imaging, projection, morphology, spatial transcriptome and manipulation of neural activity to figure out the roles and functions of dark neurons.

Imagery rescripting and targeted memory reactivation in insomnia disorder

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Insomnia disorder (ID) is the most prevalent sleep disorder causing significant daytime impairment. While standard cognitive-behavioral therapy for insomnia (CBT-I) is the primary treatment, approximately 30% of patients do not respond, highlighting the need for new therapies. In this context, the development of new non-pharmacological methods to reduce hyperarousal in these patients represents a key therapeutic target for this disorder. This single-blind, proof-of-concept, randomized controlled trial aims to recruit 120 insomnia patients aged 18 to 45 to evaluate the efficacy of imagery rescripting (IR), a specific cognitive therapy where individuals vividly imagine a negative memory and transform it into a positive one, and targeted memory reactivation (TMR), a technique that pairs an odor with a positive scenario imagined during IR which is practiced daily in bed during the evening or night. Patients will be randomly assigned to one of four experimental groups: sleep hygiene with water (SH), sleep hygiene with odor alone (OA), IR with water (IR), and IR with odor (TMR). All participants will undergo an inclusion process, four weekly intervention sessions (SH or IR), pre- and post-intervention polysomnography, cognitive tasks and questionnaires. We hypothesize: i) that the IR group will show significantly reduced insomnia severity (as measured with Insomnia Severity Index, primary outcome measure) compared to the SH group after four weeks, demonstrating IR's efficacy, ii) that the TMR group will exhibit greater reductions in insomnia severity compared to the IR group, demonstrating TMR's efficacy. Finally, we expect these reductions to be sustained at a three-month follow-up.

Challenges in Assessing Long-Term Memory for Second Language Vocabulary with Fast Periodic Visual Stimulation and EEG: Issues of Reliability and Learning Effects

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Developing efficient tools for measuring neural markers of long-term memory is an important goal in cognitive neuroscience. A promising paradigm entails the presentation of regular but infrequent visual stimuli, i.e., oddballs, that are embedded in fast periodic visual stimulations (FPVS). Neural activity related to the processing of FPVS-oddballs are evident in peaks in the power spectrum of EEG recordings at the oddball presentation frequency. Nevertheless, it remains unclear whether the information derived from such paradigms can also provide valid and reliable measures of long-term memory processes. We investigated this question in the context of long-term memory for newly learned second language (L2) vocabulary. Healthy native German or French adult speakers (N = 102) learned 48 Finnish (L2) words using a dedicated mobile app over two weeks. Participants completed pre- and post-learning FPVS-oddball tasks to measure lexical and semantic access to newly learned L2-vocabulary. In the task measuring lexical access, regular and oddball stimuli were both words and nonwords. In the task measuring semantic access, regular and oddball stimuli were words describing both manmade or natural items. Preliminary results suggest low test-retest and split-half reliabilities, as well as an absence of effects of language learning on brain activity during semantic and lexical oddballs. Our findings align with previous studies highlighting inconsistencies when using the FPVS-oddball paradigm to assess visual word recognition. Potential explanations for these discrepancies include design and language heterogeneity. We emphasize the need for standardized guidelines and pre-registration of future studies to ensure reliable and comparable results.

Impulsivity linked to amphetamine-induced sensitization and reduced dopamine D2 autoreceptor function

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Impulsivity is a multidimensional trait linked to drug abuse vulnerability due to its high prevalence among drug abusers. It is associated with a deficit in D2/3 receptors (D2/3R) in the striatum and midbrain**,** as well as hyperreactivity of the dopamine (DA) system. The D2 autoreceptor (D2-autoR) modulates DA neuron activity in the ventral tegmental area (VTA) and DA release in the striatum. Deficits in D2-autoR in VTA DA neurons may be neurological markers of impulsivity that confer vulnerability to drug abuse. We investigated whether impulsive animals exhibited high amphetamine (AMPH) sensitization associated with neuroadaptation of D2-autoR in VTA DA neurons. We used Roman High-Avoidance (RHA) and Roman Low-Avoidance (RLA) rats, which exhibit high vs. low impulsivity, respectively, and high vs. low psychomotor and neurochemical responses to acute AMPH. Additionally, using Wistar rats, the original strain for RHAs and RLAs, we examined whether these strains show neurobiological and behavioral traits that make them more susceptible or resilient to developing behavioral sensitization compared to their original strain. Rats underwent a three-week AMPH sensitization paradigm or vehicle control treatment. Ex vivo electrophysiology to record D2-autoR activity was conducted 10 days after the last AMPH injection. In another cohort of rats, impulsivity was measured with the 3-choice-serial-reactiontime task (3CSRTT) before they underwent the AMPH sensitization paradigm. DA release in the nucleus accumbens (NAc) was assessed using fiber photometry during the paradigm and 10 days after the last injection. Results showed that RHAs and Wistars exhibited higher impulsivity and AMPH-induced locomotor sensitization compared to RLAs. AMPH-induced locomotor sensitization was linked to decreased D2-autoR function in RHAs and Wistars, but not in RLAs.
Preliminary results indicated that DA release might not be affected by AMPH-sensitization paradigms. These findings suggest that impaired D2-autoR function in animals with higher impulsivity may underlie their increased vulnerability to drug abuse.

Periodic limb movements during sleep and 5-year cognitive decline in the older general population (HypnoLaus Sleep Cohort Study)

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Introduction: The relationship between periodic limb movements (PLMS) during sleep and cognitive decline remains understudied. This study examined associations between PLMS and cognitive decline over 5 years in community-dwelling older adults participating in the HypnoLaus Sleep Cohort Study.

Methods: We included 386 older adults without dementia (mean age 71.0±4.1 years, 43.3% men). Participants underwent an overnight polysomnography and a neurocognitive assessment at baseline, followed by a second neurocognitive assessment 5.2±0.6 years later. PLMS measures of interest were the PLMS index (<30/h [reference] vs. ≥30/h [n=117, 30.3%]) and the PLMS arousal index (<5/h [reference] vs. ≥5/h [n=105, 27.2%]). Linear regressions examined the associations of PLMS measures with annual change in composite scores assessing executive function, language, and verbal memory, controlling for age, sex, education, and apolipoprotein E4 (ApoE4). The moderating effects of age, sex, education, and ApoE4 were examined.

Results: In the whole sample, participants with a PLMS index ≥30/h showed a greater decline in executive function (β=-0.25, p=0.010) compared to the reference group. PLMS index ≥30/h was associated with greater decline in verbal memory in ApoE4 carriers (β=-0.44, p=0.013), but not in ApoE4 non-carriers (β=0.17, p=0.143). PLMS arousal index ≥5/h was associated with a greater decline in executive function in less educated participants (β=-0.40, p=0.006), but not in those with higher levels of education (β=0.13, p=0.333). We found no moderating effect of age or sex.

Conclusions: PLMS measures may predict cognitive decline in community-dwelling older adults, particularly among ApoE4 carriers and those with lower levels of education.

Neural representations underlying self and conspecific action-outcomes during joint decision-making in observing mice.

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Social cognition plays a crucial role in the collective success of groups by enabling individuals to learn from the actions and outcomes of their peers and integrate this information with environmental context. Previous studies have shown that neurons in the frontal cortex of socially interacting mice represent various social behaviors, but it remains unclear if these circuits are involved in observational reinforcement learning during goal-directed tasks.

To investigate this, we adapted the two-armed bandit task into a joint setting where demonstrator and observer mice alternately foraged for water in a dynamically changing environment. Initially, mice were trained in a head-fixed, two-alternative forced-choice (2AFC) setup to forage for water. We then paired expert demonstrator mice with relatively naïve observer mice to determine if observers could be influenced by conspecific cues on a trial-by-trial basis. Our data indicate that mice utilize conspecific action-outcome cues to guide their decision-making and infer correct choices. To further understand joint behavior, we developed and fitted various reinforcement learning models, finding that social models more accurately explained joint foraging behavior.

cFOS TRAP experiments validated increased activity in the frontal regions of mice observing conspecifics during the joint foraging task. Chronic recordings from these regions using dense silicon probes revealed neurons coding for multiple task features, including stimuli, rewards, and actions for both the self and conspecifics. Ongoing analysis and experiments aim to dissect the representations of conspecific action-outcomes in the frontal regions of the mouse brain, complemented by high-speed filming techniques.

Refining Clinical Trial Design: Patient & Public Involvement (PPI) in a large-scale RCT for Cognitive Rehabilitation in Multiple Sclerosis

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Background and aim. Progressively emerging in healthcare studies, Patient and Public Involvement (PPI) supports the development of evidence-based and patient-oriented research projects, thereby offering new perspectives to improve patient care in future research. We integrated a PPI in the preparatory phase of an international clinical randomized controlled trial (RCT), to enhance the quality and clinical impact of its experimental design.
Methods. This RCT will compare the efficacy of the exergame intervention Body Brain Trainer (BBT) to two other computerized cognitive rehabilitation interventions for patients with multiple sclerosis (pwMS): the tablet version of the BBT (tBBT) and the RehaCom software. The primary outcome of the study is cognitive complaints, evaluated with a patient-reported outcome measure (PROM). One of the secondary outcomes is fatigue, also evaluated with a PROM.
Patient representatives (n=6) involved in the PPI provided feedback on the experimental arms and outcomes measures of the study through a home-made survey. Clinicians (n=4) also completed a survey on the primary outcome measure.
Experimental arms – Patient representatives tested the three interventions and rated their adherence and satisfaction towards each of them, using a 5-points Likert scale questionnaire.
PROMs on cognitive complaints – Four PROMs on cognitive complaints (MSNQ, WMQ, PDQ-20 and CFQ) were evaluated on clarity and perceived relevance by patient representatives and clinicians, using a 5-point Likert scale questionnaire.
PROMs on fatigue – Three PROMs on fatigue (MFIS, FSMC and FSS) were similarly evaluated by patient representatives.
For the final decisions, two researchers in clinical neuroscience assessed the clinical relevance of these PROMs. Statistical analysis included median values and mean standard deviation, represented by spider radars and boxplots.
Results.
Experimental arms – Five patient representatives preferred the intervention BBT over the two active controls. BBT (4.42 ± 0.72) and RehaCom (4.31 ± 0.44) received higher ratings on adherence and satisfaction compared to tBBT (4.06 ± 0.31).
PROMs on cognitive complaints – The PDQ-20 (4.75 ± 0.27) was preferred, with low variances in the mean ratings, indicating good agreement among the patient representatives. The other PROMs also received overall high ratings: CFQ (4.54 ± 0.29), MSNQ (4.33 ± 0.47), WMQ (3.83 ± 0.70). Clinicians similarly favored the PDQ-20 (4.5 ± 0.54) over the other questionnaires: CFQ (3.94 ± 0.85), MSNQ (4.31 ± 0.24), WMQ (3.69 ± 0.38).
PROMs on fatigue – The MFIS (4.07 ± 0.74), FSMC (4.33 ± 0.73) and FSS (4.23 ± 0.43) received comparable high ratings from the patient representatives. Subsequent research team discussions favoured the FSMC.
Conclusions. This PPI provided valuable insights on the experimental arms and study outcomes, helping to refine the design the RCT. The future participation of collaborating centers will increase the number of patient representatives, thereby complementing the findings.

Exploring noradrenergic signaling and sleep patterns in prodromal stages of Alzheimer's disease mouse models

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The onset of Alzheimer disease (AD) and the onset of abnormal sleep patterns are both signaled by initially minute but ultimately disastrous physiological malfunctions of the brain. Amongst these, the Locus Coeruleus (LC) belongs to the primary brain areas that show such malfunctions in the early stages of AD. The LC generates large noradrenaline (NA) signals that are key for the architecture of sleep in mice. In contrast, how LC malfunctions relate to sleep disturbances in AD remains unknown.

We explore the real-time functionality of the noradrenergic system during AD's prodromal phase in an established AD mouse model using dual fiber photometric measurements in freely behaving animals that express biosensors for free NA levels in thalamus and for neuronal Ca2+ fluctuations in LC neurons. In combination with polysomnography (EEG/EMG), we record local field potential (LFP) activity in somatosensory cortex (S1) and in the hippocampus (CA1) to assess vigilance states in mice aged 2-9 months.

We currently investigate sleep architecture parameters such as the time spent in each vigilance state and bout durations, with a focus on excessive fragmentation in both light and dark phases. We track how Ca2+-activity in the LC and its NA output in thalamus relate to sleep properties. Preliminary data indicate that the Novel Object Location test is a useful measure for evaluating the animals' cognitive abilities.

Decoding the patterns of LC's dysfunction during the prodromal phase of AD and its consequences on sleep could prove essential to early diagnosis of AD and for potential interventions.

Dynamical analysis of stochastic spiking neuron models via diffusion approximations

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Recent advancements in brain recording techniques have enabled the simultaneous recording of spiking activity from hundreds to thousands of individual neurons. Effective modeling and interpretation of such data is key to understand the neural dynamics that govern brain functions. A powerful model to relate spiking activities to sensory and behavioral variables, as well as spiking history, is the nonlinear Hawkes process with inputs. However, the stochastic point process and non-Markovian nature of Hawkes processes makes their direct analysis challenging.

In this study, we employed a diffusion approximation to transform a non-linear Hawkes process into a system of coupled stochastic differential equations. We then studied the dynamics and bifurcations of the deterministic part of the approximating system using tools from dynamical systems theory. For single neurons, the corresponding fixed points are given by a closed-form solution, offering an intuitive understanding of its long-term behavior. The full stochastic system can be approximated with moment closure methods, which further explains unstable behavior in bistable regimes. Extending this approach to multiple neurons, we could analytically determine the fixed points of the corresponding deterministic part of the neuronal network dynamics, predicting their stability and revealing low-dimensional coordination during tasks. Systematically adjusting the auto- and cross-history coupling kernels allowed us to uncover the most flexible regimes, as indicated by the number of fixed points, enabling the fitting of richer dynamics.

Applying this method to spiking neural activity recorded from the human superior temporal gyrus during speech processing, we demonstrated that the dynamical properties of each fixed point could be monitored throughout the behavioral task. This revealed transient changes in the qualitative nature of these fixed points as speech envelope increases. To validate our approach, we used statistical scores such as the Kolmogorov-Smirnov test to assess the goodness of fit and confirm the accuracy of our results.

This work introduces a novel and promising approach to fitting and analyzing the dynamical regimes underlying spiking activity in neurons and neuronal networks, potentially connecting low-dimensional neural dynamics to behavioral factors.

Towards investigating salience: modulation of Locus Coeruleus – Awake auditory fMRI

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Sensory stimuli, including auditory, visual, or tactile inputs, have the capacity to evoke varied brain and bodily responses contingent upon their novelty and salience levels. Human functional magnetic resonance imaging (fMRI) studies have delineated brain regions involved in salience detection, suggesting a feedforward propagation of brain activity from sensory to associative areas. Longstanding theories have emphasized the significance of the Locus Coeruleus – Norepinephrine (LC/NE) system in governing the levels of salience in sensory signals. However, causal evidence linking LC activity to alterations in stimulus response at the brain network level is currently lacking. A common paradigm to study the novelty/salience value of a stimulus is the oddball task, where infrequent target stimuli (oddballs) are embedded in a sequence of frequent, non-target stimuli (standards). This study introduces a novel experimental methodology integrating awake functional MRI in a rat model with an oddball sensory task alongside concurrent optogenetic modulation of the LC. For image acquisition, we employ a conventional EPI sequence and initial observations indicate successful habituation of animals to the scanner environment with minimal motion artifacts. Additionally, robust BOLD activity in sensory areas was observed through the implementation of sensory stimulation paradigms using a block design.Experiments performing concurrent optogenetic activation of the LC paired with sensory stimuli are ongoing and preliminary results point towards changes in activity in both sensory and frontal areas, underscoring its role in attentional processing.

Identifying new pH-sensing residues involved in the gating of acid-sensing ion channel 1a (ASIC1a).

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Acid-sensing ion channels (ASICs) are H+-gated Na+-permeable channels. Rapid acidification occurs in synapses during neuronal activity. ASICs are widely expressed in the nervous system and have many physiological and pathological functions, such as pain sensation, fear sensing and neurodegeneration after ischemia. ASIC1a is the most H+-sensitive subunit expressed in the central nervous system. Acidification leads to protonation of a number of extracellular residues, inducing conformational changes that lead to channel activation. Identifying the protonation sites is essential to better understand the activation mechanism of ASIC channels. Mutations of a large number of titratable residues in several regions of ASIC1a affected the pH dependence, but still resulted in channels that retained the ability to open in response to acidification, suggesting the possible existence of additional pH-sensing residues. Here, we predicted new pH-sensing residues of ASIC1a by a computational approach, which calculate on the basis of the crystal structure the pKa values of titratable amino acid residues of the membrane-inserted and hydrated protein. Predicted residues were mutated to different residues to determine which biochemical side chain properties are important for their functional role. By pairing mutations of close residues, their interaction was investigated. This analysis identified several glutamate, aspartate and some histidine and lysine residues as part of H+-sensors in different key regions of ASIC1a.

Assessing emotional underpinnings of prosocial motivation

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Prosocial decision-making and behavior involve navigating the intricacies between social/moral preferences (e.g. collective well-being) and self-benefited preferences (e.g. financial gains). The two types of preferences are inherently challenging to objectively compare, which limits our grasp of the underlying psychological mechanisms. To overcome this challenge, we employ emotional reward as a metric to examine the influence of these distinct preferential dimensions on prosocial behavior across individuals, where the diversity of the participants is also captured by various relevant psychosocial traits, including altruism.

In vivo CRISPR systems for functional interrogation in neurodevelopmental disorders.

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Neuronal migration is a critical process in cortical development, frequently disrupted in neurodevelopmental disorders, including Focal Cortical Dysplasia (FCD). Despite the identification of several mutations in protein-coding genes, the absence of robust in vivo functional studies to assess arrays of targets limits a comprehensive understanding of the causative mechanisms governing cellular and molecular alterations in neuronal migration disorders. Using the developing mouse cortex as a model system, we implement cutting-edge CRISPR-Cas9-based genetic tools for efficient in vivo downregulation and upregulation of target genes, with the primary objective of elucidating the functional implications at cellular and molecular level. Combining CRISPR perturbation with single-nucleus sequencing, we were able to link each perturbation to its transcriptomic response, allowing us to obtain high-resolution molecular insights to investigate the causes of cortical malformations. These findings set the basis for future in vivo experiments to simultaneously investigate the molecular impacts of multiple genetic targets.

Role of the gut microbiota-derived metabolite TUDCA in a mouse MCAO stroke model

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Stroke is a leading cause of mortality and long-term morbidity, with ischemic stroke accounting for 87% of cases. Limited available treatments highlight the need to identify new therapeutic strategies. The bidirectional crosstalk between the gut microbiota and brain, plays a critical role in regulating the immune and circulatory systems and metabolism. Emerging studies have underscored the significant impact of the gut-brain axis and intestinal flora-derived metabolites in modulating stroke outcomes. In this study, we aim to investigate the effects of pre- and post-treatment with Tauroursodeoxycholic acid (TUDCA), a secondary bile acid conjugated with taurine, on stroke progression in a rodent model of middle cerebral artery occlusion (MCAO). Mice were subjected to MCAO and injected with TUDCA (100 mg/kg) or vehicle (PBS) via the tail vein one hour before the surgery. Lesion volume was measured using cresyl violet-stained brain slices, and neurological function was assessed using the 28-point Neuroscore. Additionally, blood-brain barrier integrity and any alteration in astrocytes and microglia 72 hours post-stroke were evaluated using immunohistochemistry staining. Our data showed no significant difference in infarct volume between the TUDCA and PBS pre-treated groups. Furthermore, evaluation of neurological deficits indicated no statistical change in the course of the experiment between the two groups. No observable gross alteration was detected in Immunoglobulin G (IgG) leakage and glial cell response following the interventions. Our findings suggest that pre-treatment with TUDCA did not exert a neuroprotective effect in the mouse MCAO model. We are currently testing administration 1 hour following the onset of ischemia.

Keywords: Ischemic stroke; gut metabolites; bile acids; middle cerebral artery occlusion; tauroursodeoxycholic acid

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EEG MARKERS TO TASK-IRRELEVANT STIMULI UNDER HIGHER AND LOWER LEVELS OF FLOW

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To characterize the neural bases of the state of flow (Csikszentmihalyi & Larson, 2014), we induced a higher versus a lower flow state in participants through two individually tailored video game play sessions, while recording their EEG.

In accord with the hypofrontality hypothesis of flow, higher flow was expected to lead to lesser frontal recruitment as it corresponds to a more automatic processing mode than lower flow. Following Castellar et al (2019), we incorporated an auditory oddball paradigm, requiring participants to respond to infrequent "target" stimuli while gaming to obtain a real-time measure of flow processes. Unlike Castellar et al (2019), we did not observe a delayed frontocentral deflection in response-locked ERPs in high as compared to low flow state. Additionally no flow state differences were observed on any of the main ERP components (N1, N2, P3 early, P3 late).

This study included 40 participants, a within-participant design and a control condition with only the oddball task. The latter allowed us to verify the high quality of the data collected and document reduced N1 to standard stimuli and P3 early to target and novel stimuli as well as a persistent P3 late to target stimuli under dual task as compared to the oddball task alone.

Overall, this study does not provide evidence for the hypofrontality hypothesis of flow, but confirms that dual-tasking comes at a processing cost visible as early as the N1 and lingering as late as 600ms as the late part of the P3 gets maintained.

Astrocyte Integration: Enhancing White Matter Numerical Substrates for diffusion MRI simulations

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Astrocytes are glial cells that play vital roles in neuronal development and contribute to repair in neurodegenerative diseases. Establishing intricate spatial connections with neurons and blood vessels, they are abundant in white matter(WM), yet tools for incorporating them into WM synthetic substrates are limited. Their imprint on the diffusion-weighted(DW) signal could however be non-negligible due to higher membrane permeability to water (than myelinated axons) and the ability to adapt their volume to maintain ion homeostasis in physiological and pathological conditions. In this study, we enhance CATERPillar, a tool for generating numerical WM substrates suitable for Monte Carlo simulations of diffusion MRI, by integrating astrocytes with axons. Drawing inspiration from methodologies like CONFIG, MEDUSA, and CACTUS, our proposed software employs chains of overlapping spheres to model and grow axons. Our focus will be on creating a realistic WM substrate based on existing literature. In a prior study, mean intracellular volume fractions (ICVFs) were given for the different cells. Literature values for density and morphology are compared to the ones achieved in CATERPillar.

CATERPillar begins by randomly placing astrocyte somas within the voxel. Axons then grow towards an attractor, while avoiding collisions with other cells. Spheres are consistently added during growth, with a placement determined by angles drawn from Gaussian distributions. Their standard deviations(std) control the tortuosity of the axons. Bead-like structures can form along axons with specified amplitude and frequency.

When encountering obstacles, the size of the added sphere gradually decreases until it fits or reaches a predefined minimum threshold. Overlaps among axons are detected using an algorithm from [10], allowing removal of colliding axons. After axon development, acquiring a myelin sheath involves inserting inner spheres within each axon sphere. Inner sphere radii are determined using an equation derived from [11], correlating inner radii with the g-ratio.

The role of anatomic connectivity in inhibitory control revealed by combining connectome-based lesion-symptom mapping with event-related potentials.

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Inhibitory control refers to the ability to suppress cognitive or motor processes. Current neurocognitive models indicate that this function mainly involves the anterior cingulate cortex and the inferior frontal cortex. However, how the communication between these areas influence inhibitory control performance and their functional response remains unknown.
We addressed this question by injecting behavioral and electrophysiological markers of inhibitory control recorded during a Go/NoGo task as the 'symptoms' in a connectome-based lesion-symptom mapping approach in a sample of 96 first unilateral stroke patients. This approach enables us to identify the white matter tracts whose disruption by the lesions causally influences brain functional activity during inhibitory control.
We found a central role of left frontotemporal and frontobasal intrahemispheric connections, as well as of the connections between the left temporoparietal and right temporal areas in inhibitory control performance. We also found that connections between the left temporal and right superior parietal areas modulate the conflict-related N2 event-related potential component and between the left temporal parietal area and right temporal and occipital areas for the inhibition P3 component.
Our study supports the role of a distributed bilateral network in inhibitory control and reveals that combining lesion-symptom mapping approaches with functional indices of cognitive processes could shed new light on post-stroke functional reorganization. It may further help to refine the interpretation of classical electrophysiological markers of executive control in stroke patients.

Keywords: Inhibitory Control · Stroke · Event-related Potentials · Lesion Symptom Mapping

Exploring the Role of Lipid Droplets in Neural Stem Cells and Their Progeny: Omics Approach

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Lipid droplets (LDs) are cellular organelles that regulate storage and hydrolysis of neutral lipids However, over the years they have been increasingly recognized for their versatility beyond energy storage. In particular, in our recent studies we have demonstrated that LDs play an important role for proper neural stem/progenitor cells (NSPCs) metabolism and proliferation (Ramosaj, Madsen et al., Nature Communications 2021), and that LDs are present in various brain cell types to a much larger extent than previously thought (Madsen et al., BioRxiv 2022). However, the functional significance of LDs in brain cells remains elusive, and it is not known if LDs differ in their composition between different brain cell types. To investigate the potential role of LDs in cellular identity, we established an LD isolation protocol using primary mouse derived NSPCs. In present study, we compare LD protein and lipid profiles among different cellular states, including proliferative NSPCs, quiescent NSPCs, and NSPC-derived astrocytes. Through isolation of LDs from each cell type and subsequent liquid chromatography-mass spectrometry (LC-MS) analysis of the extracted proteins and lipidomic analysis of the lipids, we aim to obtain a comprehensive LD proteome and lipidome dataset spanning different states of NSPCs, ranging from quiescence to differentiation. This will allow us to shed light on the functional role of LDs in NSPCs and their progeny.

Cardiac interoception and insular cortex: a pathway to understanding social deficits in autism

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Cardiac interoception (CI) is the ability to sense and interpret internal cardiovascular signals, particularly those of the heart. It plays a crucial role in social interactions by helping develop a sense of self in relation to others. This process is particularly relevant in the context of Autism Spectrum Disorder (ASD), where social deficits are a core feature. Understanding the root causes of these deficits is challenging due to the complexity of social interactions. This study explores CI as a potential contributor to social impairments in ASD. It hypothesizes that altered CI, influenced by emotional states and modulated through Heart Rate Variability (HRV), plays a significant role.

The first aim is to investigate the neuronal mechanisms of CI, with a focus on the insular cortex, where interoceptive signals, initially processed in the nucleus of the solitary tract, are integrated. We simultaneously monitor neuronal activity in the posterior insular cortex and heart rate regulation during social interactions by employing fiber photometry and telemetry. Preliminary findings in control animals indicate distinct activation patterns in insular cortex neurons and heart rate responses during non-social and social behaviors, particularly those with negative valence. This research provides novel insights into the neural and cardiovascular interplay during social encounters. State-of-the-art techniques as telemetry, fiber photometry, and behavioral analysis, are employed to elucidate the relationship between CI and social behavior, potentially aiming at finding interventions for mitigating social impairments in ASD.

Cognitive Immunity: a novel paradigm of neuro-immune modulation

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Through evolution, social species have developed a series of behavioral responses, such as social distancing, aimed at preventing contacts and thus infections, which is termed behavioral immune system (BIS). Here we investigate how the BIS anticipates potential encounters with virtual infection threats and interacts with the biological immune system to elicit an anticipatory response.

We propose that the engagement of the predictive function of the brain in sampling the environment to trigger adaptive behavior is an integral component of immunity and is exploited to detect potential pathogens even before they enter the physical barriers of the body and to anticipate and mount a preparatory immune defense. We have developed virtual reality (VR) approaches in humans and behavioral conditioning protocols in mice to simulate virtual infections and trigger neuroimmune responses. Currently, we are characterizing the behavioral, physiological, neural, and immune responses in both human and murine models to decipher mechanistic interactions and identify targetable molecular pathways. We aim to discover and characterize in detail the signaling processes and pathways that, from sensory processing of anticipatory pathogen detection, especially in social contexts, trigger behavioral processes of pathogen avoidance and immune processes towards pathogen elimination.

Our project opens novel perspectives for the development of VR-based solutions to trigger, measure and modulate immune functions via virtual immune threats with important potential biomedical and clinical applications.

Revisiting contextual fear processes using a novel social conditioned place aversion protocol

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Context processing is an essential function in the cognitive repertoire of numerous species, including humans and mice, allowing them to learn from their environment and adapt their future behavior. Impairments or alterations in contextual processing are hypothesized to be at the core etiology of psychopathologies such as post-traumatic stress disorder (PTSD). Current treatment options for anxiety- and trauma-related disorders are limited, mainly due to gaps in our knowledge regarding underlying brain circuits. These gaps are exacerbated since most conclusions from basic research were derived from fear conditioning protocols using electric shocks as unconditioned stimuli. Yet, as social stress is an omnipresent and ethologically relevant stressor for social species, protocols in animal models based on social trauma can reveal brain circuitries and neurotransmitters/-modulators that are particularly sensitive and thus, pertinent for translational interventions. Here, based on social defeat paradigms, we developed a novel social conditioned-place aversion (sCPA) protocol in adult mice. Our data revealed that whereas most mice learnt to avoid the context where they repeatedly received aggression, a small subset of animals did not show a clear avoidance. Interestingly, our analyses indicated that avoidance indices did not correlate with the amount of aggression received. Thus, it is possible that other factors, such as individual differences in anxiety-like behavior or in valence attribution to positive or negative cues, could account for this variability. Developing and validating a social trauma-based conditioning protocol will aid to study stress vulnerability aspects and allow us to dissect the brain circuit involved in contextual processing.

Assessing the Generalizability of an HCP Connectome Harmonization Model

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Data harmonization is crucial to mitigate heterogeneity in multi-site neuroimaging studies and thereby enhance statistical power and generalizability. A factor contributing to such heterogeneity is the variability in acquisition parameters (APs) of the data collected across sites. While there is no gold standard in designing a harmonization model, information regarding APs makes valuable prior knowledge to improve performance. In this work, we have designed such a model to harmonize structural connectomes (SCs).

The training dataset consisted of 600 SCs derived from T1-weighted images and resampled diffusion imaging data (b-value = 1000 and 3000 s/mm2 and isotropic spatial resolution = 1.25 and 2.3 mm, modeling a cohort scanned across 4 sites) of the Human Connectome Project Young Adult (HCP-YA) dataset. Linear regression was proposed with explicit modeling of b-value and spatial resolution to correct this acquisition bias at the level of SCs. The performance of this model was validated on an independent clinical dataset. This independent validation dataset consisted of the T1-weighted images and diffusion weighted images of 11 healthy subjects from the Lausanne Psychosis Cohort. The diffusion imaging data included diffusion tensor imaging (DTI), bval = 0 and 1000s/mm2, as well as diffusion spectrum imaging (DSI), maximum b-value = 8000 s/mm2. The DSI data was resampled to have maximum b-value as a factor of variation (3000, 5000 and 8000 s/mm2). The above linear regression model was used to harmonize DTI-derived SCs to DSI-derived SCs at the three modeled maximum b-value settings.

Although our simple regression model was trained on the high-quality HCP-YA dataset, it generalized to a different clinical dataset. While it was trained to harmonize DTI data from b-value = 1000 to 3000 s/mm2, it also efficiently harmonized DTI data at b-value = 1000 s/mm2 to DSI data until a maximum b-value of 5000 s/mm2, demonstrating generalizability and robustness. Hence, simple models should not be disregarded completely for more complex ones, especially when it comes to clinical applications.

Associations Between Blood Markers of the GSH Redox cycle and Brain White Matter Microstructure

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In groups of patients suffering from psychosis, redox dysregulation was reported in both peripheral fluids and the brain. It has been hypothesised that such dysregulation, including alterations of the glutathione (GSH) cycle could participate in the brain white matter (WM) abnormalities in schizophrenia (SZ) due to the oligodendrocytes' susceptibility to oxidative stress (OxS).
In this study we aim to assess the differences between 99 psychosis patients (PT) and 86 healthy controls (HC) in GSH-redox peripheral blood markers: GSH peroxidase (GPx), reductase (GR) and their ratio (GPx/GR-ratio), evaluating the hypotheses that alterations in the homeostasis of the systemic GSH cycle may be associated with pathological mechanisms in the brain WM in PT. We also consider the hypothesis that different homeostatic states of the system (oxidative vs reductive) may reflect differently into the WM microstructure. To do so, we employ the advanced diffusion MRI methods: Diffusion Kurtosis Imaging (DKI) and White Matter Tract Integrity-Watson (WMTI-W), which provide excellent sensitivity to demyelination and neuroinflammation.
We show that GPx levels are higher in female participants and modulate the effect of aging on the WM. We found differences between PT and HC in the association of GR and mean kurtosis (MK). Namely, lower MK was associated with higher blood GR activity in HC, but not in PT, suggesting that high GR activity (a hallmark of reductive stress) in HC was linked to changes in myelin integrity. Remarkably, GSH-redox peripheral blood markers did not explain the WM anomalies detected in PT.

Perinatal adversity and sulcal morphometry mediate the association between parental age at birth and psychopathology in offspring

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Parental age at birth is a known risk factor for a wide range of psychopathological conditions in offspring. Simultaneously, it is associated with various gestational, obstetric, and birth complications. Given the critical role of the perinatal period in the onset of psychiatric disorders, we hypothesized that the effect of parental age on psychopathology is mediated by the perinatal adversity it triggers. Sulci, which develop during the fetal period and remain stable after birth, serve as a valuable proxy for perinatal neurodevelopment in postnatal ages. Analyzing sulcal morphometry can help us understand the impact of perinatal adversity on brain maturation.
Methods : We leveraged data from the ABCD Study, a longitudinal investigation into the developmental determinants of mental health among 11,897 children. Comparing different modelisation approaches, we explored :

- Parental age at birth and behavioral problems (Child Behavior CheckList) and emotional regulation (Emotional regulation questionnaire)
- Parental age and perinatal adversity (gestational, obstetric and birth complications)
- Parental age and sulcal surface, length, opening and mean depth.
- Mediation effect of perinatal adversity and sulcal morphometry
- Covariates included sex, age, age of the other parent, level of education, household income, psychopathology of each parent. Additional modelisation while controlling parenting style and children perceived support were also performed.

Results : At 9-11 years old, maternal and paternal age at birth was related to CBCL scores and CBCL above pathological threshold, both in a quadratic way, children born from younger and older parents having more behavioral problems. Maternal age was linearly and positively associated with sulcal surface and mean depth in frontal and parietal regions. Paternal age was linearly and positively associated with sulcal surface, length and mean depth in frontal regions, an effect present only in boys in sex specific analyses. Emotional regulation analyses, perinatal adversity analyses, additional modelisation and mediation are still ongoing.

Neuroanatomical investigation of hippocampus and amygdala structure in a mouse model of Williams syndrome

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Williams syndrome (WS) is a rare genetic neurodevelopmental disorder with unique cognitive and behavioral profiles. It has an incidence of 1 in 7,500 – 20,000 live births and is due to a hemizygous deletion of about 26 genes on chromosome 7. Individuals with WS exhibit severe visuospatial and allocentric spatial learning deficits, over-friendliness and poor social inhibition. These hallmark characteristics raise questions about the neurobiological substrates of cognition and social behavior in WS. Behavioral and neuroimaging studies indicate functional alterations in the hippocampus and amygdala of individuals with WS, two critical regions for spatial memory and social processing, respectively. My thesis aims to provide quantitative data on the cellular organization of the hippocampus and amygdala in a mouse model replicating the hemideletion found in more than 90% of individuals with WS. I will use design-based stereological analyses on 50- µm thick Nissl-stained brain sections to provide estimates of the volume, neuronal number and soma size of the main hippocampal regions and amygdala nuclei of mutant and wild type mice. Given the conserved structural organization and functions of the hippocampus and amygdala across species, neurobiological alterations associated with the WS genetic deletion should be manifest in this mouse model. Consequently, by providing estimates of the cytoarchitectonic characteristics of the hippocampus and amygdala, my work will unveil whether, and how, the WS hemideletion impacts the structural integrity of the hippocampus and amygdala, and contribute to elucidating the genotype – phenotype relationship in individuals with WS.

Psychometric validation of a naturalistic test for Theory of Mind after brain injury: final results

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Aims: The ability to infer someone else's mental states (i.e., the Theory of Mind; ToM) is essential for navigating the social world. ToM impairments may compromise socio-professional reintegration, yet they are typically underestimated in patients with acquired brain damage (ABI). Therefore, sensitive and ecological tools are needed for the neuropsychological assessment of social cognition in this population. A systematic review from our group identified the Movie for the Assessment of Social Cognition (MASC) as a promising tool with good ecological validity and strong psychometric properties in psychiatric populations. The purpose of this study is to validate this test in ABI patients.

Methods: Participants: 20 patients (> 3 months post-stroke or traumatic brain injury) presenting with a social cognition deficit (OSCARS [3]), 20 age/sex/education-matched controls.
Procedure: comprehensive neuropsychological assessment of social cognition including the MASC.

Results: MASC scores reliably discriminated patients from controls ($d = 1.58$, $p < .001$). Patients' performance was characterized by hypomentalizing errors, i.e. underestimations or incomplete estimations of someone's mental state. Other psychometric criteria (convergent validity, sensitivity/specificity, test-retest reliability, and internal consistency) were fulfilled.

Conclusion: The MASC showed excellent psychometric performance in ABI patients. These results set the stage for an ecological neuropsychological assessment of social cognition in patients with acquired brain injury, but also in other neurological conditions.

Brain Stimulation To Optimise treatment in Physiotherapy – Low Back Pain (STOP- Low-Back Pain) : A study protocol

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Introduction : Non Specific Chronic Low Back Pain (NSCLBP) is a burden for the society. Multidimensional factors are involved in NSCLBP and neurophysiological modifications have been observed. Particularly, changes in structure and function of the Pre Frontal Cortex have been documented. Transcranial Direct Current Stimulation (tDCS) is a promising device to modify brain activity and have been used in the treatment of persistant pain. The effects of tDCS on NSCLBP are not yet demonstrated, but the combination of tDCS over the Dorso-Lateral Pre Frontal Cortex (DL-PFC) and physiotherapy seems to be encouraging.

The Primary aim of this Randomised controlled trial is to compare the effectiveness of a combination of tDCS over DL-PFC and Active Physiotherapy to the combination of Sham tDCS over DL-PFC and Active Physiotherapy on multidimensional impact of pain.

Method and analysis: Forty height participant (24 per group) with NSCLBP will be randomised into two groups (tDCS + Active Physio, sham tDCS+ Active Physio) to receive 9 session of their allocated intervention. The primary Outcome will be the multidimensional impact of pain assessed at baseline, 4, 12 and 24 weeks. Secondary Outcomes will include Kinesiophobia, Anxiety and Depression, Function, functional cortical connectivity, and flexion relaxation phenomenon.

Ethics and dissemination: Ethics approval was obtained was obtained from the Comission Cantonale d'éthique de la recherche Genève (CCER) in December 2022 (2022-D0077).

The results of the study will be submitted to a peer reviewed journal and scientific meetings.

Effects of phase-encoding on BOLD data with a positive control task

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Quality assessment and quality control (QA/QC) checkpoints layered throughout the dataflow are essential to ensure the reliability of neuroimaging analyses. In the case of functional MRI, best practices recommend collecting a 'positive control' task with which the different layers of QA/QC can be validated. These are short and simple tasks designed to elicit robust and precisely located brain activation patterns, permitting the diagnosis of potential issues in the workflow. Here, we examine how the phase-encoding direction (PE) choice in echo-planar imaging (EPI) blood-oxygen-level-dependent (BOLD) fMRI influences the resulting activation maps using a positive control task that includes visual and motor paradigms.

Parvalbumin interneuron-mediated modulation of gamma oscillations and cerebrovascular tone in awake mice while at rest

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Gamma oscillations are essential for various cognitive functions such as attention, perception, memory, motor control, and synaptic plasticity. Importantly, disruption of these synchronized oscillations is linked to cognitive impairment disorders. Concurrent neurophysiological and hemodynamic recordings in humans and animals reveal a strong correlation between gamma-band power and cerebral blood flow (CBF) during stimuli and rest, suggesting CBF reflects neural network activity. However, the neuronal mechanisms behind this correlation, particularly involving Parvalbumin (PV) interneurons responsible for generating gamma oscillations, remain unclear. Our study proposes that PV neurons generate both gamma rhythms and spontaneous vascular fluctuations, explaining the hemodynamic correlation with gamma power.

Using transgenic PV-cre mice (3 females and 3 males, 3-4 months old), we selectively expressed hM4Di-DREADD-mCherry or m-Cherry alone in PV neurons in the somatosensory cortex (S1). Deschloroclozapine (DCZ) administration (100 ug/kg) was used to enhance Gi signaling. Two-photon microscopy recorded calcium (Ca2+) dynamics with virally expressed GCaMP8f and vessel diameter changes with injected vascular dye. EEG bone screws measured gamma power. The administration of DCZ significantly decreased the frequency of Ca2+ events in PV neurons (from 2.620.17 events/min to 1.680.07 events/min, Mixed Design ANOVA, $p<0.01$) but increased it in non-PV neurons (from 1.660.11 events/min to 2.830.11 events/min, Mixed Design ANOVA, $p<0.01$), suggesting efficient suppression of inhibitory PV neuron activity by DCZ, leading to elevated network activity. Notably, DCZ injection did not significantly change the average amplitude of Ca2+ events. DCZ also reduced the power of high-frequency oscillations, including gamma, and increased the power of low-frequency oscillations, particularly in the 1-4 Hz band. Moreover, DCZ injection dilated the basal artery, making it less vasoactive. In contrast, no significant differences were observed in control. Our results suggest spontaneous vascular fluctuations are largely modulated by ongoing PV neuron activity, with PV-cell signaling potentially explaining the high hemodynamic correlation with gamma activity.

Gut-Derived Tryptophan Metabolites enhance Th17 Cell encephalitogenicity in experimental autoimmune encephalomyelitis and are associated with increased NfL levels in persons with Multiple Sclerosis

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Introduction: The gut-brain axis is an emerging factor in multiple sclerosis (MS) and experimental autoimmune encephalomyelitis (EAE). Persons with MS (PwMS) and mice with EAE exhibit intestinal dysbiosis linked to disease severity. Myelin-specific Th17 lymphocytes infiltrate the colonic lamina propria, gaining encephalitogenic properties before reaching the central nervous system. We propose that gut-derived metabolites promote myelin-specific Th17 pathogenicity in EAE and are associated with disease severity in MS.
Methods: Using the adoptive Th17 cell transfer EAE mouse model, we characterized myelin-specific Th17 colonic immune cells by flow cytometry and RNA sequencing. We performed untargeted metabolomics analysis of fecal filtrates from mice treated or not with antibiotics. Myelin-specific Th17 cells were exposed in vitro to microbiota-derived metabolites. Serum Neurofilament light chain (sNfL) levels were assessed, and untargeted metabolomics of plasma samples was performed in PwMS. Spearman correlations between metabolites and sNfL levels were calculated.
Results: Gut-derived metabolites treatment of myelin-specific Th17 cells in vitro enhances their pathogenicity and promotes their encephalitogenic properties in vivo, aggravating EAE severity. Several gut microbial-derived metabolites were altered in the fecal metabolome between control and antibiotics-treated mice. We identified microbiota-derived tryptophan metabolites associated with EAE severity in mice and increased NfL Z score levels in PwMS. Treatment of Th17 cells with tryptophan metabolites enhanced their encephalitogenic properties.
Conclusion: Microbiota-derived tryptophan metabolites induce a pathogenic switch in Th17 cells, enhancing their encephalitogenic abilities. These metabolites play a key role in intestinal dysbiosis during neuroinflammation, offering therapeutic insights for PwMS.

Connectivity score allows cell-to-cell communication analysis of the hypothalamic network controlling reproduction.

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Gonadotropin hormone-releasing hormone (GnRH) neurons represent the last layer of the hypothalamic network controlling the HGP axis and reproduction. In mice, the development of this network is characterized by complex biological processes, including embryonic migration and cell-to-cell communication for the establishment and postnatal maturation, which triggers the onset of puberty. In sexually mature animals, this network shows structural and functional plasticity to support the estrous cycle and adapt reproduction depending on environmental conditions. Despite the numerous studies that have been instrumental in identifying key players in this process, the underlying cellular and molecular mechanisms remain elusive.

To address this, we decided to leverage the growing availability of single-cell transcriptomics studies and build an in silico tool to investigate cell-to-cell communication (CCC) in the mouse hypothalamus in basal condition and after metabolic challenge (Hypomap). CCC is inferred using a complex communication score based on (i) gene expression of validated Ligands-Receptors pairs in the source and target cell populations, (ii) neuroanatomical connectivity of source and target cell populations based on viral tracing experiments, (iii) functional annotation of signaling pathways in the source and target cell populations.

Interestingly, we found that hypothalamic cell communication is influenced by sex and profoundly modified by metabolic status. Unfortunately, GnRH neurons were not represented enough in this dataset for a meaningful analysis. However, our tool efficiently depicted cell communication of various cell populations influencing GnRH neuron activity, including Kisspeptin neurons, astrocytes, and tanycytes. Further work is aimed at prioritizing and functionally validating the best candidates identified by this study.

A role for the subthalamic nucleus in aversive learning

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The subthalamic nucleus (STN) is critical for behavioral control; its dysregulation consequently correlated with neurological and neuropsychiatric disorders, including Parkinson's disease. Deep brain stimulation (DBS) targeting the STN successfully alleviates parkinsonian motor symptoms. However, low mood and depression are affective side effects. STN is adjoined with para-STN, associated with appetitive and aversive behavior. DBS aimed at STN might unintentionally modulate para-STN, causing aversion. Alternatively, the STN mediates aversion. To investigate causality between STN and aversion, affective behavior is addressed using optogenetics in mice. Selective promoters allow dissociation of STN (e.g., Pitx2) vs. para-STN (Tac1). Acute photostimulation results in aversion via both STN and para-STN. However, only STN stimulation-paired cues cause conditioned avoidance and only STN stimulation interrupts on-going sugar self-administration. Electrophysiological recordings identify post-synaptic responses in pallidal neurons, and selective photostimulation of STN terminals in the ventral pallidum replicates STN-induced aversion. Identifying STN as a source of aversive learning contributes neurobiological underpinnings to emotional affect.

Modulating food ratings with gamified inhibitory control training

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High Body Mass Index (BMI) is a risk factor for several diseases such as diabetes and cardiovascular diseases. On a behavioral level, a high BMI is associated with low inhibitory control and high “wanting” for food rewards. In this project, we thus investigated how food “wanting” can be modified through inhibitory control training (ICT) in individuals with various BMI. From pre- to post-training, in the experimental group compared to the control group, we expected a decrease in “wanting” for high-calorie foods. The ICT consisted of participants playing a game designed to reinforce intrinsic motivation, engagement, and adherence, thus creating a satisfying experience. Unlike most studies in the field that only provide a single training session, this game enables daily training over weeks, at home. We compared an experimental training group in which high-calorie foods are associated with motoric inhibition and a control group in which both high- and low-calorie foods are associated with motoric inhibition. As the difference between the experimental and control training conditions lies only in the stimulus-response (SR) mapping proportions, participants in both conditions do the same task and expect the same outcomes. This control of participants’ expectations is another major asset of this approach. Preliminary results (n=16) suggest that the effect of training on food ratings is different between groups from pre- to post-tests ($F(1, 1493.8) = 6.03$, $p<.05$). These two groups are currently still under a double-blind procedure. In sum, we are investigating whether inhibitory control training could result in a devaluation of high-calorie foods.

Striatopallidal cannabinoid type-1 (CB1) receptors determine innate defensive behaviors

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Survival requires the selection of appropriate behaviours in response to threats, and dysregulated defensive responses may trigger maladaptive coping underlying anxiety and post-traumatic stress disorder (PTSD) conditions. Threat-induced behaviours, including freezing (passive) and flight (active), are controlled by multiple neuronal circuits; however, the mechanisms controlling the active-passive trade-off in defensive responses have only been scantly investigated. The endocannabinoid system, and particularly cannabinoid type-1 (CB1) receptors in striatal direct and indirect pathways, has been proposed to participate in this effect, but the neuronal basis of this interaction has not been addressed. Herein, we used a combination of a naturalistic looming-sweeping task, computational behaviour tracking, pharmacogenetics and viral approaches to gauge the contribution of different striatal subpopulations of CB1 receptors in orchestrating APT during innate or acquired paradigms. We found that, while striatonigral CB1 receptors are not involved in regulating defensive responses, escape behaviours require the activation of CB1 receptors specifically located at striatopallidal terminals (indirect pathway). Functional manipulations revealed that specific targeting of striatopallidal CB1 neurons is sufficient to reinstate the ability to cope with threatful stimuli. These observations indicate a new mechanism by which striatopallidal CB1 receptors regulate coping responses and pave the way for a better understanding of neural circuits involved in defensive behaviours.

Regional changes in density and spatial distribution of calbindin- and parvalbumin-expressing neurons in the developing mouse brain

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The brain undergoes major reorganization and development during adolescence, involving dynamic changes in the number and distribution of various cell types. Neurons expressing the calcium-binding proteins parvalbumin and calbindin are widely distributed across the adult brain, and during development, they contribute to the maturation of neural networks underlying a range of functions, e.g. fear memory processing and social behavior. However, information about the number and distribution of calbindin and parvalbumin cells in the developing mouse brain is fragmented, with most studies investigating only one or a few brain regions. We here present a comprehensive collection of microscopic image data from the developing mouse brain (postnatal days 9, 14, 21, and 35), immunohistochemically stained for calbindin and parvalbumin. Images were spatially registered to age-specific volumetric brain atlases, allowing quantification of calbindin and parvalbumin cell numbers using the QuickNII-ilastik-Nutil (QUINT) workflow provided by the EBRAINS research infrastructure (https://ebrains.eu/services/atlases). Our study focuses on areas of the mouse brain associated with social behavior (including the hypothalamus and insular cortex) and fear memory (including the basolateral amygdala, pre-, and infralimbic cortex). However, all data resulting from the project will be publicly shared through the EBRAINS research infrastructure, thus allowing researchers to investigate regional changes in mouse brain architecture through adolescence across the entire brain. Funded from EU Horizon 2020, Specific Grant Agreement No. 945539 (Human Brain Project SGA3).

Encoding of speech modes with varying articulatory and phonatory properties; an EEG/ERP Investigation

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To overcome obstacles in verbal exchanges, speakers use speech modes that are specific prototypes of speech with variations in phonatory and articulatory features (Zhang & Hansen, 2007). Nevertheless, the Direction Into the Velocities of Articulatores (DIVA) model from Guenther (2016) does not provide a mechanistic account of the encoding of atypical speech (Tourville & Guenther, 2011; Weerathunge, 2022). Therefore, we investigated the electrophysiological signature induced by loud speech and a new speech mode which is imitation of an english accent. We hypothesized that both speech modes will be encoded differently because of the type of representations on which they vary. 24 neurotypical french speakers produced pseudowords in a delayed production task with high density EEG recording. After standard preprocessing steps, we averaged epochs of 350 ms (i.e., 179 TF) into event related potential (ERPs) aligned in the backward manner to the vocal onset. Waveform amplitudes analyses and Topographic Analysis of Variance (TANOVA) revealed differences in the last 150 ms preceding the vocal onset for each speech mode relative to standard speech. The Microstates analysis demonstrated that while the imitation condition required the activation of an additional brain network to produce pseudowords, loud speech and standard speech only differed in the distribution of the same Microstates. Source localization of the additional Microstate showed that motor/prefrontal regions were involved. The present results indicate that different speech modes entail either specific changes in brain dynamics of the same processes or implication of an additional network in the 150 ms preceding vocal onset.

Investigating Lexico-semantic Representations in Artificial and Biological Neural Networks: an Optimization Loop

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Understanding where and how semantic representations are encoded in the brain remains a fundamental question in cognitive neuroscience. Neuropsychological and causal lesion studies highlight localized hubs for semantic processing, including the anterior temporal lobe and posterior middle temporal gyrus. However, recent correlation findings using natural speech experiments and large-language model (LLM) embeddings implicate a distributed set of cortical regions. To reconcile this contrasting evidence, we hypothesized that neural representations underlying lexical semantic concepts could be causally modulated by optimized stimuli. We performed intracranial recordings of a patient with epilepsy who read aloud from the French book ”Le petit prince”. In parallel, we generated the LLM embeddings for the same sentences and correlated them with the neural data using regression methods. Next, we identified words that could maximize the activation of neural data. The patient read these optimal words aloud the next day, and we analyzed the corresponding neural responses.

In this initial experiment, conducted with one patient, no increase in neural activity in response to the optimized words was observed. This could be due to various factors, including suboptimal word selection methods, repetitions, limited data, and inadequate regression methods. We have investigated solutions to address these issues and plan to conduct an updated experiment.

While these preliminary results are inconclusive, our research will clarify the localized versus distributed perspectives, which is crucial for developing personalized rehabilitation protocols for stroke patients with language deficits.

Estimating lifestyle, genetic and biological risk factors contributing to Alzheimer's disease and dementia

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Dementia is a significant global health challenge, characterized by a decline in cognitive function to the extent that it interferes with independence in daily activities. Currently, over 55 million people are affected worldwide, with 10 million new cases each year. The age-specific incidence of dementia has declined in many countries, probably due to improvements in education, nutrition, health care, and lifestyle changes suggesting that dementia prevention is possible. Therefore, a further decrease of dementia can be achieved through dementia prevention plans in persons at risk of dementia. There are biological, genetic, and potentially modifiable lifestyle risk factors that can contribute to increased dementia risk. Therefore, risk profiling of cognitively unimpaired individuals based on these risk factors can inform personalized and targeted dementia prevention interventions. However, an accurate estimation of the contribution to dementia of each of these risk factors accounting for each other is still lacking. Additionally, a comprehensive cumulative risk assessment that combines lifestyle, biological, and genetic risk factors remain to be developed. This study aims to accurately assess the adjusted hazard ratio of lifestyle, biological and genetic factors on dementia incidence in population-based cohorts of cognitively unimpaired individuals. The risk calculation will be conducted by one of the two primary methodologies under consideration: collecting data from relevant systematic reviews and meta-analyses published in peer-reviewed journals and analyzing their data or directly analyzing the data of large epidemiological cohort studies from diverse populations. This study will provide precise estimations of the adjusted risk of each dementia risk factor which are pivotal for calculation the adjusted dementia risk for individuals and enhance the development of personalized risk reduction interventions to reduce the global burden of dementia.

Neural decoding from deep brain electrodes to support closed loop therapies in Parkinson's patients

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Despite impressive advances in neuromodulation therapies for Parkinson's disease (PD), a big majority of patients with advanced PD develop disturbances of gait and balance, including postural instability, festination, or freezing of gait, that are refractory to existing treatments. These deficits lead to frequent falls and increase comorbid conditions. Closed-loop stimulation therapies of brain and spinal cord have the potential to better address locomotor abnormalities. However, the delivery of stimulation must be tuned online to the fluctuating state of patients, as well as to task- and context-related constraints encountered in daily life. Such closed-loop therapies are contingent on biomarkers that inform about locomotor activities and deficits in real-time. Here, we aimed to leverage the neural sensing capabilities of last-generation neurostimulators for deep brain stimulation to (i) identify neural biomarkers that underlie locomotor function and dysfunction in the subthalamic nucleus of PD patients, (ii) characterize changes in these biomarkers under different therapeutic conditions (medication, DBS), and (ii) prototype a modular decoding framework that is able to robustly predict locomotor states and deficits despite fluctuations and real-life constraints. We recorded 35 participants with advanced PD implanted with DBS, and we thoroughly characterized the changes induced by LDopa and DBS on gait biomarkers, across a variety of locomotor tasks of daily life. We found distinct modulations in low-beta, high-beta and Gamma bands that encoded locomotor states such as sitting, standing and walking. Gait encoding across these frequency bands responded differently to DBS and LDopa, which hindered the performance of a single neural decoder across different therapeutic conditions. We leveraged these observations to design a modular framework that automatically selects among two neural decoders in real-time, based on condition-specific neural correlates. This modular framework robustly coped with therapy-related fluctuations. Considering the large number of patients treated worldwide with DBS implants, as well as the capabilities of newest commercial stimulators, our work pave the way for the possibility of controlling the stimulation in closed-loop neuromodulation therapies that address gait deficits in everyday life conditions.

Disentangling error signals in Purkinje cell dendritic activity from their pre-synaptic climbing fiber inputs during sensory association and adaptive motor learning

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Sensorimotor adaptation, crucial for refining movements in response to unexpected errors, fundamentally depends on the cerebellum. The olivary climbing fiber (CF) input to cerebellar Purkinje cells (PC) acts as a "teacher" signal during motor learning and drives cerebellar plasticity. Although the CF input reliably evokes PC dendritic spikes, it is not the only signal that modulates this post-synaptic response.

To disentangle the modulation of the pre-synaptic CF burst from that of its post-synaptic PC dendritic response, we simultaneously imaged PC dendrites and CF terminals with 2-photon microscopy in lobules V/VI/Simplex of the mouse cerebellum during spontaneous activity, movement or sensory evoked responses and sensory, reward and sensorimotor prediction errors. Mice performed either an active motor adaptation or passive association task. In the active task, mice were trained to push or pull a robotic manipulandum and adapt their forelimb movements to unexpected assistive or resistive force perturbations. In the associative task, the forelimb was passively displaced by the manipulandum in response to an auditory go cue, followed by a reward. Prediction errors were introduced by intermittently omitting either the cue, limb movement, or reward.

Our preliminary results reveal fundamental differences in how CF and PC dendritic activity are modulated spontaneously and in response to different forms of sensory, motor or reward related signals and prediction errors. These results allow us to infer the functional significance of plasticity mechanisms that occur in the CF-PC synapse itself.

From pre- to post-natal brain asymmetry: callosal contribution and relationships with cognitive and genetic factors

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The human brain, despite initial symmetry, exhibits intriguing asymmetrical features. Strong associations have been established between brain asymmetry and corpus callosum structure. Prenatal brain asymmetries appear around 11-13 weeks of gestation, reflecting early genetic-developmental left-right axis formation. These asymmetries affect cognitive and socio-emotional processes, with implications for neurodevelopmental and psychiatric disorders. However, the developmental trajectory of brain asymmetry from prenatal to postnatal stages, its interaction with corpus callosum integrity, and its effects on cognitive and socio-emotional development remain unclear.
This study aims to trace anatomical brain asymmetry from pre- to postnatal periods in typically developing (TD) children and those with corpus callosum dysgenesis (CCD). Using longitudinal, multimodal data from Lausanne and Geneva University Hospitals, it will evaluate relationships between callosal biomarkers, cognitive and socio-emotional development, and genetic origins. The study includes T2-weighted foetal brain MRI scans acquired between 20-35 gestational weeks and follow-up data (T1-weighted MRI, neuropsychological tests, questionnaires and saliva DNA sampling) at school age (6-12 years) from 90 children (60 TD, 30 CDD) born between 2012 and 2021.
Brain images will be segmented using FoetalSynthSeg and SynthSeg to calculate hemispheric asymmetry indexes. Genetic analysis will focus on TUBB3 Single Nucleotide Polymorphisms (SNPs), linked to callosal formation and brain asymmetry. Random effects models will assess group differences and asymmetry maturation. Associations between asymmetry indexes, cognitive and socio-emotional outcomes, and SNPs will be examined using sparse partial least squares correlations.
This study leverages unique longitudinal data to enhance understanding of brain asymmetry development and its relationships to cognition and genetic variations.

Mobility in atypical parkinsonism: a randomized trial of physiotherapy

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Background: Parkinson's Disease (PD) in advanced stages and atypical parkinsonian disorders (APD), such as Multiple System Atrophy (MSA) and Progressive Supranuclear Palsy (PSP), share the same typical symptoms of gait impairment and reduced mobility. These gait difficulties and postural instability are associated with reduced capability of walking. Which often leads to sustained disability, reduced quality of life and is linked to higher morbidity and mortality rates. To treat these gait difficulties, physiotherapy sessions are known to be helpful and are thus prescribed to the patients. However, there have been no controlled studies that addressed whether gait-specific physiotherapy in Parkinson-variant MSA and PSP is superior to standard physiotherapy.

Objective: This double-blind randomized controlled trial compares guideline-conform gait focused physiotherapy (GPT) and guideline-conform general therapy, or "standard" physiotherapy (SPT) and matching homebased exercises in improving the mobility in parkinsonian disorders including PD, MSA-P and PSP-RS. But also, to develop sensor-based machine learning algorithms that provide objective metric data for the clinical rating of motor signs.

Methods: Standard physiotherapy intervention comprises exercises for stretching and mobilization, light transfer tasks, rotational tasks, posture training, balance exercises and walking tasks. Whereas the gait-focused physiotherapy has particular focus on strength, balance, and variations of gait training. Both interventions will take place for 2-weeks and followed by a 5-week unsupervised gait-focused home-based training. For the algorithm development, there will be a 7-day home monitoring phase, where patients will use the wearable sensors at home daily – once right after the first visit and once right before the last visit.

Results/Conclusion: The project will provide evidence-based recommendation for treatment of gait disorders through physiotherapy, in atypical Parkinson disorders such as MSA and PSP.

Autoregressive Graph Convolutional Network as Foundation Model for Behavior Prediction

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Foundation models are trained on large-scale data on an unsupervised learning task, and subsequently adapted to downstream tasks. This technology enabled the emergence of ChatGPT, and might be a promising approach to the development of imaging biomarkers of behavior.

In this work, we explored whether we can leverage a foundation model to train a downstream model on the task of predicting age, gender, and four different behavioral dimensions. We used 979 subjects with resting-state functional magnetic resonance imaging data on the Human Connectome Project Young Adult dataset. We trained a Chebnet, a type of graph convolutional network, on the task of autoregression as our foundation model on 685 subjects, using 147 subjects as a validation set. Subsequently, we extracted a number of features and trained a ridge regression as a downstream model on another set of 147 subjects. This was done in a cross-validated manner, splitting the data randomly for 100 iterations. As a baseline, we compared model performance to predicting the same targets directly from functional connectivity. We additionally investigated how scaling the number of subjects and sessions changes the performance of foundation and downstream models.

The downstream model predicted age and gender with a similar performance as the baseline model, but neither downstream nor baseline model predicted the behavioral dimensions above chance level. The scaling experiments showed that while autoregression performance was at an optimum training on just one session, downstream performance benefited from having more than one session available to generate features.

Brain mechanisms of ego- and allocentric representations in VR-based imagined and actual navigation

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Every day we need to navigate and be aware of our location. Previous studies showed differences in brain mechanisms between two typical navigation strategies- egocentric (body-centered coordinates) and allocentric (world-centered coordinates) reference frames. However, it is not clear whether and how we rely on different strategies in imagined navigation during route planning, and how brain mechanisms differ between imagined and actual navigation in virtual reality (VR) environments.

We recruited 17 right-handed young healthy participants to undertake VR navigation tasks. Two participants were excluded: one experienced dizziness in the VR environment, while another demonstrated poor spatial navigation skills (accuracy below 70%). Fifteen participants (9 females) were ultimately included.

From the behavioral level, we found no significant difference in reaction time between ego- and allocentric conditions, which suggested the function of imagination in spatial navigation. The high accuracy rates exceeding 80% in both egocentric and allocentric conditions indicate robust spatial navigation abilities among the participants. The fMRI results showed that egocentric representation showed similar brain activation for imagined and actual navigation, mainly in the precentral gyrus, postcentral gyrus, and superior parietal lobule. Allocentric representation relied more on the fusiform gyrus and lingual gyrus during actual navigation than during imagined navigation.

Brain-controlled spinal cord stimulation for lower limb rehabilitation

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A spinal cord injury (SCI) interrupts the communication between the brain and the spinal cord, resulting in sensory, autonomic and motor deficits below the level of the lesion. Applying electrical epidural stimulation (EES) over the lumbosacral region of the spinal cord can reactivate the dormant, yet functional, motor neurons that control lower limb muscles and produce walking. In the context of the STIMO-BSI study (NCT04632290), a patient with chronic SCI, who had already undergone EES assisted neurorehabilitation, was implanted with 2 electrocorticogram (ECoG) devices to establish a digital bridge between the brain and the stimulation system implanted over his spinal cord. The brain signals are wirelessly streamed and decoded in real-time through classification algorithms, which generate online predictions of motor intentions. We are able to classify motor attempts of different lower limb joints with high accuracy. The decoded predictions are then translated into electrical stimulation commands and wirelessly delivered to the neurostimulator targeting the dorsal roots of the spinal cord, with a latency of below 1 second and allowing safe and long-lasting prosthetic use of the BSI. The study represents a proof of concept of the implementation of the BSI. Moreover, neurorehabilitation with the BSI supported neurological recovery as assessed through a battery of clinical evaluations. The patient is now able to independently use the system at home and the signal shows long term stability after 2 years. In a new clinical study (Think2Go, NCT0624395) we want to evaluate the effectiveness of the fully-implantable Brain-Spine Interface in patients with severe chronic SCI who had not undergone EES neurorehabilitation before. We implant one WIMAGINE® device (64 ECoG electrodes) over the leg sensorimotor cortical area, paired with the purpose built ARCIM lumbar system (Onward medical).

Stimulation of astrocytes in the neurogenic niche of the dentate gyrus

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Adult neurogenesis is a process by which hippocampal neural stem cells (NSCs) proliferate and produce new and functional neurons. This process is observed in two regions of the mammalian brain, the subventricular zone and the dentate gyrus of the hippocampus. In the hippocampus, adult neurogenesis is involved in learning and memory.

Interestingly, the direct cellular environment of NSCs, the neurogenic niche, provides major neurogenic cues. In particular, astrocytes play a crucial role in several steps of adult neurogenesis including NSC proliferation, new neurons' survival and synaptic integration.

In order to further investigate the role of astrocytes on the regulation of adult neurogenesis, we used a novel viral approach to target the expression of activating Designer Receptor Exclusively Activated by Designer Drugs (DREADD) specifically in astrocytes. Using calcium imaging, we verified the appropriate targeting of astrocytes and DREADD functional expression in these cells. We then used this approach in vivo to control the activity of astrocytes in the dentate gyrus and examine their role in the regulation of adult hippocampal neurogenesis. The goal of this study is to test the possibility that artificially activating astrocytes may increase adult neurogenesis and hippocampal function.

These investigations will enable a better understanding of the regulation mechanisms of adult neurogenesis in the hippocampus by the neurogenic niche. These mechanisms are relevant to hippocampal function and diseases, such as Alzheimer's disease and mood disorders.

Characterising goal obstructiveness and uncertainty through changes in behaviour, physiology and brain activity

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UNIGE

The nature of emotions and their neural underpinnings remain debated. Here we study whether appraisal theories may account for the differentiation of emotional states and their functional organisation in the brain. This theory proposes that events are perceived and evaluated according to distinct cognitive dimensions (appraisals) that are key to eliciting the range of emotions we experience. Appraisals trigger changes in behaviour, physiology, and brain activity patterns. Building on a previous study, we manipulated the appraisal of goal obstructiveness during a first-person video game. 55 participants played this game while undergoing fMRI. Behavioural measures i.e. sum of inverse distance to all enemies and player's projected distance were extracted as an indirect measure of goal obstructiveness.The fMRI data were preprocessed using fMRIPrep. Participants completed personality questionnaires, including the Beck Depression Inventory (BDI). We conducted Partial Least Square Correlation (PLSC) analyses to establish links between personality questionnaires and functional connectivity. Functional connectivity matrices were constructed for each level of each behavioural measure. Beck Depression Inventory scores emerged as the most significant contributor to personality score loadings within this latent component.General Linear Model (GLM) with parametric modulators allowed us to examine brain activation patterns associated with changes in behaviour. The modulated regressor served as the psychological regressor in subsequent Psychophysiological Interaction (PPI) analysis. Functional images were parcellated to derive 419 regions. Each of these regions were used as a seed, with each of the remaining regions as targets. Distinct connectivity patterns related to different behaviours were found.

Predictive representations for rapid learning of complex tasks via composition of behavioral primitives

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Animals exhibit an astonishing capacity to rapidly adapt their behavior to novel challenges. We show that such adaptability is made possible by combining two cornerstones of biological intelligence: (1) the ability of the brain to predict how the world changes as a consequence of behavior and (2) the fact that behavior can be generated by composing together multiple smooth behavioral primitives with high predictability. We simulated an agent that learns complex tasks according to these two principles. In the first phase, the agent gradually builds a predictive representation (PR) of the consequences of following sequences of behavioral primitives. In the second phase, the desired task is solved via gradient descent by composing differentiable behavioral primitives. Crucially, most of this goal directed learning can be performed offline (i.e. without having to execute actions in the real world), using the predictive representation to simulate the real world while also providing an analytical expression for the gradient of the loss function. We show that this division of labor allows extremely sample-efficient learning that is several orders of magnitude faster than model-free RL. Finally, we show that in order for the behavioral primitives to be useful, their spatiotemporal complexity must strike a balance: primitives must be complex enough to move the agent through the environment efficiently, yet sufficiently simple to ensure their predictability.

Plastic brain mechanisms supporting reduction in cravings induced by response training

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Recent evidence indicates that interventions involving the repeated inhibition of motor responses to environmental cues reduce brain reward responses and craving for these cues, and in turn their consumption. Such approaches have been put forward as a promising solution to unhealthy food overconsumption.
Yet, the neurocognitive mechanisms underlying inhibition training to reduce reward responses remain largely unknown.
We will address this question with a randomised controlled trial examining how Go/NoGo training reduces implicit motivational and electrophysiological activity to trained sugary drink cues. We will then examine if computational indices of Pavlovian and Reinforcement learning biases moderate the efficacy of the training, to test how inhibition training involves affective learning mechanisms.

What is long-term memory? Investigating the neuronal structures and molecular mechanisms of memory storage in engram cells.

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BMI-EPFL

Memory is the capacity of an organism to acquire, store and recover information based on experience. In the brain, experiences that become memories appear as enduring changes only in a small set of activated neurons, called engrams.

While the mechanisms of how such memories are deposited in engrams for short periods of time has received considerable attention over the past decade, the current knowledge of how memories are stored in engram cells in the long run is still scarce. Consequently, this project aims to identify the mechanisms based on which a memory becomes remote by integrating a wide range of analyses, from morphological to biochemical and molecular aspects of engram cells.
We perform contextual fear conditioning on a TRAP2 mouse model, which enables to obtain an activity-dependent genetic labeling specifically of engram cells. For morphological changes, we analyze dendritic spines and synapses using confocal and transmission electron microscopy, respectively. For biochemical changes, we will characterize histones post-translational modification with mass spectrometry, and for molecular changes, we focus on transcriptional and epigenomic signatures with single-nuclei RNA-seq coupled with ATAC-seq and/or CUT&Tag.

Since previous studies that have indicated that memory storage cannot reside solely at the level of dendritic spines and synapses, whose turnover is too fast to account for the stability of remote memories, and since epigenetic mechanisms can stably register experience-dependent cellular activity states for example in development, we hypothesize that epigenetic mechanisms might provide a nucleus-based solution of lasting enough nature to explain the basis of long-term memories.

Autoencoders, PCA and ICA as reconstruction and feature extraction tools in whole-brain functional connectivity data

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The increasing possibility of accessing medical data from all over the world and its increasing complexity put a challenge on the creation of algorithms that can guarantee a quick and clear diagnosis. In this project, we tackle the well-known ”curse of dimensionality”, having a dataset of schizophrenic patients and compatible healthy controls that contains only 292 subjects, but counts 9730 whole-brain functional connectivity features per subject. Hence, the need for a feature extraction algorithm that proves to be able to extract a reasonable amount of features and still guarantees the right diagnosis in binary classification. Our first aim is to investigate whether autoencoders, which are increasingly employed in feature extraction applications, could be a suitable solution for our particular problem. We also exploit well-established methods, like PCA and ICA, both to be a touchstone for autoencoders and to check how well they could perform in our case. Up-to-date Bayesian optimization techniques were employed. In this project we compare the performance of PCA, ICA, a shallow autoencoder, and a deep AE across varying numbers of extracted features. The optimization of the classification hyperparameters favors SVM with a polynomial kernel and ICA-reduced dimensionality with accuracy at 71% on original dataset and 91% on augmented dataset. Notably, Independent Component Analysis consistently outperformed other methods in feature selection, highlighting its effectiveness in the context of schizophrenia diagnosis. Despite the potential of advanced techniques such as Deep Autoencoder, based on our analysis, simpler methods such as ICA should not be neglected.

Index Terms—Unsupervised Learning, Autoencoders, PCA, ICA, Connectivity matrix, Brain data analysis.

Neurohormonal markers of stress in Borderline Personality Disorder: interplay between oxytocin and cortisol

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Borderline personality disorder (BPD) is characterized by important emotion dysregulation, particularly in response to psychosocial stressors. Emotions (mainly anger and sadness) may therefore be felt and expressed more intensively. Stress response involves cortisol and oxytocin, which are released by the adrenal glands and by the pituitary gland, respectively. A previous pilot study carried-out by our group has shown that oxytocin displays less variation in naturalistic setting and lower reactivity during a stress task in patients with BPD when compared to healthy controls. We are now carrying out a larger trial to better understand the interplay between hormonal markers (cortisol and oxytocin). We aim to recruit 80 patients with BPD and 80 healthy controls. Each participant will go through three visits including: psychological assessment, endogenous salivary measures of cortisol and oxytocin in a naturalistic environment and under a psychological stress task (TSST). Our purpose is to better understand the interplay between cortisol and oxytocin in everyday life and during laboratory stressor, but also which other factors may influence these hormonal changes like medication, hormonal contraceptives, childhood adverse events and other psychiatric comorbidities. Our study may offer a better understanding of the neurobiological processes involved, which may help to contribute to the development of new psychotherapeutic and pharmacological approaches.

Oxytocin mediates social collaboration in a cortical-amygdala network

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Social interaction is a fundamental pillar of our society. It has made possible extraordinary achievements such as going to the moon. In humans, a rare autosomal disease characterized by calcification of the basolateral amygdala (BLA), revealed the importance of the BLA and its connections to the medial prefrontal cortex (mPFC) in generous investments. However, the neural mechanisms underlying social interactions that lead to fruitful cooperation remain largely unknown. In this study we address the role of the prosocial neuropeptide oxytocin in neural circuits between the mPFC and the BLA involved in collaboration. Although oxytocin receptors have been found in both regions, its precise location and its effect on social collaboration remain to be determined. Using a transgenic rat line expressing CRE under the oxytocin receptor promoter in combination with viral labeling we found that cells expressing the oxytocin receptor were located throughout the anterior cingulate, prelimbic and infralimbic cortices. In vitro patch clamping recording furthermore showed that action potential firing rate of oxytocin receptor cells increased when an oxytocin agonist was added to the bath. Current work aims to determine whether oxytocin can directly affect neuronal activity of cells projecting from the mPFC to the BLA, suggesting that oxytocin signaling modulates the neuronal circuitry between the mPFC and the amygdala. Furthermore, we implemented a new behavioral task in which two rats must cooperate to obtain food in order to study the social communication behavior of rats and to determine how oxytocin can influence the success of a cooperation.

Preclinical Study of Pituitary Gland Microstimulation for Oxytocinergic Neuromodulation of Social Behaviour

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Mental health disorders affect a significant portion of the global population, highlighting the need for innovative therapeutic approaches. Rodent research suggests oxytocin (OT) could address mental health challenges due to its role in social behavior and fear modulation. However, translating animal findings to humans faces challenges such as inefficient OT delivery across the blood-brain barrier and the absence of methods to induce OT release in the human brain.
To overcome these limitations, we aim to establish a translatable rodent model for electrical stimulation evoking central OT release, facilitating human trials led by our clinical partners. The main goal is to determine whether electrical stimulation of structures easily accessible in humans (such as the pituitary) can evoke OT release in central brain areas.
We performed electrical stimulation of the pituitary stalk in anesthetized rats, which is known to elicit antidromic action potentials in the paraventricular nucleus of the hypothalamus (PVN). By using novel adeno-associated viral vectors (rAAVs) that lead to the expression of GCaMP6s under the control of the OT promoter we performed simultaneous fiberphotomety-based calcium recordings of OT neuron populations in the PVN.
Preliminary findings revealed that electrostimulation of the pituitary stalk evoked rapid calcium transients peaking approximately 2 seconds after stimulation onset, consistent with cytosolic calcium influx followed by sodium current based antidromically generated action potentials. As these results are based on genetically identified OT neurons they extend previous electrophysiological findings, which were naïve of the neuronal genetic identity. Further, they provide a proof of concept that our experimental manipulation can indeed evoke OT neuronal activation.
In ongoing experiments, we utilize a novel OT sensor to to measure pituitary stimulation-induced OT release in brain regions implicated in emotional regulation. Our investigations may support experimental interventions in humans, offering innovative treatments for mental health disorders.

Abstract # 127

Dopaminergic and glutamatergic mechanisms of cranial nerve stimulation in rat fear learning models

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Neurons in the brain communicate via complex electrochemical signaling processes involving release and reuptake of neurotransmitters. This electrochemical signaling enables vast neural networks to perform complex brain functions. Advances in silicon probe technology now allow us to monitor the electrical signaling within these complex networks with high spatial and temporal resolution. However, we currently lack the technology to study neurochemical signaling with equivalent precision, leaving us unable to fully understand neurotransmitter roles across a range of key neuroscience and psychology questions, and to relate these data to those obtained with electrophysiology. This PhD project is embedded in a larger interdisciplinary collaboration that is using nanotechnology in combination with enzymatic and aptamer biorecognition methods to develop an innovative biosensor that can monitor a range of neurotransmitters with high sensitivity and fast temporal resolution. The novel real-time biosensor will focus on dopamine and glutamate signaling. Using this biosensor, as well as validated standard methods such as awake fast-scan cyclic voltammetry, this PhD project will focus on the mechanisms and effects of cranial nerve stimulation in rat fear learning and fear extinction models. The project has just started, and we are currently conducting the first experiments. At the time of the summer school, we will be able to present the first 9 months of research that have been done using the new biosensor and fast-scan voltammetry.

The making of a Lewy Body: An ultrastructural study of Parkinson's Disease pathology in post-mortem human brain and an iPSC-derived cell model.

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Lewy Bodies (LBs), aggregates rich in the protein alpha-synuclein (aSyn), are a major pathological hallmark of Parkinson's disease (PD). Despite existing descriptive studies of LBs in human post-mortem brain, we are only beginning to understand the mechanisms that underly LB formation. Cellular models are critical in answering these questions, as they allow the survey of inclusion formation in real time. Recently, iPSC-derived human dopaminergic neurons (iDAs) seeded with PFFs were shown to develop aSyn-rich inclusions, but few ultrastructural comparisons of iDA models with post-mortem PD brain tissue exist. Using room-temperature correlative light and electron microscopy, we characterised the ultrastructure of various stages of LB pathology in midbrain dopaminergic neurons of two PD-diagnosed donors. Second, we compared them with aSyn-rich inclusions in a PFF-seeded iDA model to assess its translational relevance. In both post-mortem and iDA inclusions, we find loosely packed fibrils associated with structures of the lysosomal-autophagosomal pathway. Strikingly, some iDA inclusions additionally contained large multilamellar structures, which were previously associated to neurodegeneration. Further, three-dimensional ultrastructural reconstructions allowed for quantification of mitochondrial and lysosomal damage. Our results are a first step towards an ultrastructural characterisation of the prion-like spreading mechanism of misfolded aSyn that is believed to underly progressive neurodegeneration.

Electrophysiological characterization of dendritic plateau potentials that are selectively mediated by higher-order thalamocortical projections in somatosensory cortex

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In the rodent primary somatosensory cortex (S1), feedforward tactile whisker information is dynamically integrated with various sources of feedback information. This generates context-dependent neuronal activity that lies at the basis of behaviourally relevant sensory percepts. While feedforward and feedback streams of information finally converge through a densely interconnected local network, they initially enter the cortex in a distinct laminar fashion. Here, various cell-types differently extend their dendritic arborisations, leading to striking differences in the extend of feedforward and feedback information that even neighbouring neurons may receive. This concept is supported by previous electrophysiological experiments in our lab showing that L2/3 cells with slender apical dendritic tufts were relatively sensitive to optical stimulation of recombinant opsin-expressing inputs from the first-order ventral posteromedial thalamic nucleus (VPM), whereas cells with broad tufts responded more strongly to the higher-order posteromedial thalamic nucleus (POm). Additionally, POm was shown to selectively enhance the excitability of the latter postsynaptic cell-type, which was associated with the emergence of dendritic plateau potentials. Various pharmacological modifications during dendritic patch-clamp recordings have linked these potentials to a G-proteïn coupled signaling cascade that culminates in the closing of two-pore domain potassium (K2P) leak channels. Currently, we are elaborating this study by verifying potassium as the driving force behind these plateau potentials. To this end, we performed dendritic patch-clamp recordings of L2/3 neurons in acute slices, while optically stimulating recombinant opsin-expressing inputs from POm. Recordings were made at varying membrane holding potentials surrounding the potassium reversal potential. Additionally, we will begin efforts to investigate if similar thalamocortical signalling mechanisms are also present in morphologically different cell-types in L5.

High-density electroencephalographic correlates of gait disorders in post-stroke patients

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Stroke causes sensorimotor impairments that disrupt motor skills performance, including balance and gait. However, the neurophysiological changes underlying this condition is still debated. This study aims to characterize alterations in the dynamics of electroencephalographic signals as biomarkers of gait disorders.
EEG signals were acquired from 20 stroke patients and 21 control participants age-matched using a high-density recording system during 14 meters of straight walking and 5 min of resting-state. Mini BESTest and Gait dynamic index were used to assess the dynamic balance and functional gait abilities, respectively. Weighted Phase Lag Index analysis was used to characterize functional connectivity within four regions: Centroparietal and Frontocentral in right/left hemispheres. Statistical analyses were performed using a t-test between groups in alpha and beta bands. Analysis between the straight walking wPLI and clinical scales were obtained through Pearson coefficient score.
A pairwise between groups t-test of straight walking task analysis revealed significant reductions of functional connectivity in stroke patients as compared to healthy participants, in both alpha and beta band. Despite these reductions in Stroke patients, few sensors couples correlate with the clinical scales. Furthermore, results a wPLI decrease at Rest compared to the task.
According to the literature, the decrease in wPLI in both bands of stroke patients at rest compared to healthy participants highlights clear alterations in functional connectivity in the stroke group. The increased connectivity observed during straight walking could be due to the task constraints that imply a reorganization of connectivity in both groups compared to the resting state. The correlation between sensor pairs and clinical assessments suggests that patient behavior may have an inverse directionality with connectivity values.
WPLI is an interesting tool for detecting abnormal changes in the dynamics of EEG signals associated with stroke. These changes are associated with the clinical outcome.

Identity of our Invisible Others: (En)facing robotically-induced presence hallucinations

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Presence hallucination (PH) – the nonveridical experience of someone close by can occur in patients with psychiatric and neurological diseases, and in healthy individuals, particularly during bereavement. PH has been associated with self-monitoring alterations by sensorimotor signals. These phenomenologically varied hallucinations are commonly anthropomorphic, with the identity of PH (iPH) perceived as that of a significant other (e.g., partner) or as an unidentified stranger. Despite its significance for people who regularly experience them, iPH remains poorly understood due to the paucity of hallucination induction methods.

Here we investigated the mechanisms of iPH in healthy subjects, by merging a robotic sensorimotor method shown to induce PH (Bernasconi et al., 2021), with a 2AFC (partner or stranger) face identity detection task, as an implicit measure of the experienced identity of iPH. Twenty-five participants in romantic relationships performed the PH-inducing sensorimotor robotic task, followed on each trial by a brief exposure to morphs between their partner's and a stranger's photograph. We successfully replicated PH induction, as participants reported feeling someone was around them significantly more during asynchronous than the synchronous stimulation ($p=0.006$). The robotic stimulation significantly modulated face perception in participants which are sensitive to such sensorimotor manipulation ($p=0.048$). After accounting for differential sensitivity, we found that in the asynchronous condition participants perceived more Partner, when there was objectively more of the Stranger's identity present ($p=0.035$). We interpret these findings as altered self-monitoring, where PH-inducing stimulation activates a closely related neural and functional representation to the self in the brain – that of our partners.

Combining on-cell patch clamp with localized muscimol puffing to reveal electrophysiological abnormalities in animal models of ASD

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Autism spectrum disorder (ASD) is a term used to describe a wide variety of neurodevelopmental disorders that share manifestations and symptoms including intellectual disabilities, social impairments, delayed speech development and repetitive behaviors. Different animal models of ASD share similar electrophysiological and morphological aberrations at the neuronal level. In particular, previous studies have shown that the developmental maturation of GABAergic circuitry appears altered leading to an excitation/inhibition imbalance in the adult. During neurotransmission, the polarity of the GABAergic response depends on the intracellular [Cl-] of the postsynaptic neuron which is elevated at birth and decreases during the postnatal development to reach adult values in a process known as “GABA switch”. In our project, the on-cell patch clamping technique allows to measure the GABAergic response without altering the intracellular [Cl-]. By puffing muscimol (selective GABAAR agonist) we detect the polarity of the GABA response and by repeating the experiment in animals of increasing ages we can monitor the progression of the GABA switch. Thanks to this technique we study the delay in temporal onset of the “GABA switch” during postnatal development in different transgenic animal models of autism such as Nlgn3 KO and PTEN. In addition, the DFGABA and spontaneous spiking frequency values are measured through on-cell patch clamping, these measurements are repeated until adulthood to verify if the observed abnormalities persist after the developmental period for GABAergic maturation is closed. The project aims to give insights into how early GABAergic defects could lead to autistic behaviors in the adult.

Unraveling the Neurogenic Niche Symphony: Hippocampal astrocytes mitigate microglial reactivity to inflammation.

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Inflammation in the brain is a hallmark of many devastating diseases, including Alzheimer's. Central to this inflammatory response are microglia, which release proinflammatory cytokines that disrupt adult hippocampal neurogenesis in the dentate gyrus, undermining the survival of hippocampal stem cells. Astrocytes, as crucial components of the neurogenic niche, actively promote neurogenesis. However, the intriguing role of astrocytes in regulating microglial inflammation within this niche remains largely unexplored.

Previous work demonstrated that astrocyte-secreted factors boost newborn neuron proliferation and survival, while microglial reactivity hinders neurogenesis, impairing cognition and memory. This study investigates whether homeostatic astrocyte-secreted factors can counteract microglial inflammation, potentially enhancing neurogenesis and restoring cognitive function.

Using in vitro hippocampal rat primary cultures exposed to neuroinflammatory stimuli (lipopolysaccharide and IFNg at 100 ng/ml), we found that astrocytes mitigate microglial inflammation. This was supported by morphological analysis, cytokine concentration measurements, and live imaging. Further exploration using 3D culture models revealed that both cell types secrete inflammation-buffering molecules. Additionally, intraperitoneal injections of astrocytic molecules in an acute inflammation mouse model reduced sickness and depression-like behavior, as well as hippocampal inflammation.

These findings highlight astrocytic molecules as key regulators of brain inflammation and suggest their potential therapeutic role in enhancing neurogenesis and cognitive function in neuroinflammatory conditions.

Postnatal structural development of the monkey perirhinal and parahippocampal cortices

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The perirhinal and parahippocampal cortices are key components of the medial temporal lobe memory system and essential for the processing of spatial and declarative memory. In humans, major changes in declarative memory capacities occur within the first seven years of life, but until recently, the neurobiological substrates underlying these changes remained hypothetical. Previous studies have shown that distinct regions, layers and cells of the hippocampus and entorhinal cortex exhibit different profiles of structural and molecular development during early postnatal life. Accordingly, the differential maturation of distinct hippocampal circuits is thought to underlie the differential emergence of specific "hippocampus-dependent" memory processes. To better understand the maturation of the primate medial temporal lobe memory system, we implemented design-based stereological techniques to characterize the structural development of the different layers and subdivisions of the perirhinal and parahippocampal cortices in macaque monkeys at different postnatal ages. We found different developmental changes in neuronal soma size, neuron number and volume of the distinct layers and subdivisions, which overall suggest an earlier maturation of the parahippocampal cortex compared to the perirhinal cortex, and an earlier maturation of the superficial layers relatively to the deep layers. These findings are consistent with studies showing the differential maturation of the rostral and caudal entorhinal cortex, which are interconnected with the perirhinal and parahippocampal cortices, respectively. This study provides fundamental information on the normal development of the primate medial temporal lobe memory system and define critical periods of maturation that might be sensitive to perturbation and contribute to developmental disorders.

The Impact of Hormonal Changes on Functional Neurological Disorder: an international online study

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Functional neurological disorder (FND) occurs more often in women than man (ratio 3:1) but there is no clear explanation for this gap. Possible factors include diagnostic biases and the higher prevalence of sexual trauma in women. Nonetheless, women with a history of sexual abuse are still more susceptible to develop FND than men exposed to comparable events and the overrepresentation of women diminishes after the age of 50, both indicating a potential role of biological factors. This emphasizes the importance of investigating the impact of sex hormones such as estrogen, progesterone, or testosterone on FND. We aim to test whether life events associated with hormonal changes (menstrual cycle, pregnancy, menopause) affect FND symptomatology. We will collect informations from patients diagnosed with FND and observe their changes in the symptoms along different hormonal phases.Suvey have been created by our team on RedCAP in 6 langages. The survey consists of different «case-scenario» were participants are asked whether they are taking an hormonal contraception, are pregnant, menopausal, have been through a gender transition or have a menstrual cycle. Then, a corresponding questionnaire focus on the change in symptoms during each event.

Plasticity on NAc LH-projectors in highly-palatable-food induced overeating

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Obesity is driven and maintained by dysregulation of appetite. Especially nowadays, with rich availability of palatable processed food, overeating promotes weight gain through unbalancing energy expenditure and intake. Lifestyle interventions are foundation of obesity management; however, the long-term maintenance is challenging. Thus, understanding the neural mechanism underlying compulsive overeating is urgent for better weight control.

Dopamine system and hypothalamus are highly involved in obesity, proved by fMRI in patients. In mice, our lab discovered that a specific subset of nucleus accumbens (NAc) D1-MSNs projecting to the lateral hypothalamus (LH) authorizes feeding. As the potentiation of NAc D1-MSNs is responsible for cocaine induced adaptive behavior, we hypothesize that plasticity on NAc LH-projectors could be also necessary for the long-term weight increase in compulsive overeating.

Here, we first observed decreased excitatory transmission on NAc LH-projectors acutely after food restriction by ex vivo electrophysiological recordings. To clarify which are the major inputs contributing to that, we performed TRIO experiment and located PVT, BLA, Xi and vHipp. Combining retrograde tagging and optogenetics in patch clamp experiments, we found reduced AMPA/NMDA on NAc LH-projectors receiving afferents from vHipp. Further, we will construct an in-cage compulsive feeding paradigm with consumption monitored automatically, and explored the plasticity on NAc LH-projectors after long-term exposure as well as abstinence to highly palatable food. We will also assess neuronal activity change during the building process of compulsive overeating.

We would like to address the interaction between plasticity and compulsive overeating, to develop better management methods for obesity.

Acute stress induced alteration of sensory representation in CeA

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Acute stress can profoundly influence our physical and mental well-being, has many effects on the brain. The central amygdala (CeA) plays a pivotal role in processing and integrating sensory information related to stressors, thereby orchestrating appropriate behavioral and physiological responses. But how acute stress induces alteration of sensory representation in CeA remains elusive. Here, we monitored different CeA cell types at single cell level and showed the coding properties of these cell types in sensory representation. CeA encodes sensory information with valence in a divergent manner, where pain information is encoded by a separate ensemble of CeA neurons. In addition, acute stress inhibits most CeA neurons and affects the response of CeA neurons to noxious stimuli. Our results suggest that CeA neurons can reorganize under acute stress, thereby affecting the response to external stimuli, which may in turn evokes the adaptive behavior of animals to the external environment.

The brain integration of affective cues in non-literal forms of speech

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Language may serve many purposes, among them, is the communication of emotions. These emotions can be conveyed in different ways in speech, either with prosody or in a lexico-semantic manner. These two types of emotional information are differently communicated, interactive, and activate some common brain regions, such as the superior temporal gyrus and the inferior frontal gyrus (Buchanan, 2000; Meyer, 2003). However, how these different cues are integrated at the brain level is still poorly understood. To better understand this semantic and prosodic integration, researchers often used the incongruity paradigm (Kotz et al., 2015; Lin et al., 2020). Indeed, when affective prosodic and semantic cues are incongruent, like in the case of sarcasm or irony, the listener needs to integrate both information to decode the intended affective message. Few brain studies investigated sarcasm and irony processing at the brain level and showed that the inferior frontal gyrus (IFG) was involved in irony and sarcasm understanding (Matsui et al., 2016; Filik et al., 2019). Moreover, some authors suggest that understanding sarcasm relies on the ability to make inferences about others' mental states, that is the theory of mind (Zhu & Wang, 2020), and activates prefrontal areas including the ventromedial prefrontal cortex (Tamir et al., 2016). In the present fMRI study, 50 participants were exposed to literal vs. non-literal forms of speech across various tasks, with their attention directed towards different cues (i.e., prosody, semantic, irony, sarcasm, and social cognition). Our findings demonstrate the involvement of the inferior frontal gyrus (IFG) across these different tasks and is therefore a potential candidate for the hub of integration of these different affective cues in non-literal forms of speech.

Plasticity in the Lateral Habenula after adult-newborn interactions

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Abstract: Parental care is essential to ensure the survival of newborns, which is not only observed in humans but also across the animal kingdom. Mice display a variety of parental actions such as nursing, pup grooming, crouching, nest building, and pup retrieval. Unlike mother and father mice, virgin mice show distinct behaviors toward pups: males tend to attack pups while females begin to care for them. Among the brain regions involved in parental care, recent data suggest a contribution from aversion-related structures, particularly the Lateral Habenula (LHb). LHb neurons are excited by aversive pup calls, and their activity is necessary for pup retrieval in virgin female mice. Additionally, the LHb exhibits sexual differentiation in various aspects. Anatomically, the innervations onto the LHb are not identical between sexes. Gene expression differs between virgin female and male mice, and their behaviors toward newborns also differ. Receptors expression related to social, mood regulation also varies: estrogen receptors are higher in female rats, while vasopressin receptor antagonist in LHb impacts social behavior in males rather than females. Based on this information, we aim to tackle two questions: First, does sexual dimorphism define cellular properties of LHb neurons? Second, do adult-newborn interactions alter LHb neuronal activity?
Here, we use whole-cell patch-clamp recording to reveal the cellular properties underlying adult-newborn interactions in LHb.

Multi-class syllable imagery decoding with Stereoelectroencephalography (sEEG)

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Brain-Computer Interfaces (BCI) aim to establish a direct pathway between the brain and an external device without involving the motor system, relying exclusively on neural signals. Recent breakthroughs have demonstrated impressive performance in real-time decoding of attempted and imagined speech with intracranial recording. Our work focuses on exploring the significant features and brain areas for decoding each imagined syllable within a natural imagined sentence. To achieve this, we designed an experiment to record intracranial sEEG signals while participants imagined pronouncing syllables, words, and sentences. The task was divided into several sub-tasks: (1) Separate imagined speech intervals from rest activity. (2) Separate syllables from imagined speech intervals (3) Build the classifier for syllable decoding.

In the first sub-task, separating imagined speech intervals from rest activity, we extracted the time-frequency representation and the power from each frequency band of each channel. We then split the data into two groups: imagined speech and non-imagined speech. We applied two methods to define the important features for decoding the imagined speech period. In the first method, we selected the important features based on random forest classifier. And we built a binary SVM classifier for decoding the imagined speech period to verify the efficiency of the important features. In the second method, we applied a contrastive learning method in the time-frequency representation in each channel and explore the important features. This structured approach allows us to identify key neural signals and brain areas associated with imagined speech, ultimately contributing to advancements in BCI technology

Differentiated roles of projections from AIC and LO to BLA in working memory and reward learning

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How cortical inputs from various regions are integrated in subcortical areas to control behavior is an essential question in systems neuroscience. Here we addressed the question focusing on cortical inputs to the basolateral amygdala (BLA), which is critical for working memory and reward learning. BLA receives inputs from the orbitofrontal cortex (LO) and agranular insular cortex (AIC), yet it is not clear how the projections from these two regions to BLA contribute to learning and memory. Anterograde tracing showed that the BLA neurons receiving projections from LO exhibited more anterior and dorsal distribution than those from AIC. We then trained head-fixed mice to perform olfactory-based working-memory task. Optogenetically suppression of delay-period activity of the LO-BLA projections in the learning phase improved task performance, whereas suppression that of the AIC-BLA projection impaired task performance. To examine neuronal encoding of learning and memory related information by these two pathways, we conducted two-photon calcium imaging of BLA neurons receiving projections from either LO or AIC. We found encoding of working-memory related information both in the BLA neurons receiving AIC projections and in that receiving LO projections. Further comparison of the differences in coding abilities of the two circuits is to be study. To summarize, the projections from the LO and AIC to BLA exert differentiated roles in learning of working-memory task, through distinct neuronal populations.

Dual lineage origins of neocortical astrocytes

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Astrocytes represent one of the most abundant cell types in the central nervous system and play an essential role in nearly all aspects of brain functions. Although they have been for long considered a relatively homogeneous cell type, the idea that cortical astrocytes could constitute a various population at morphological, molecular and functional level, has been increasingly entertained in the last decade. Despite these recent advances, how this diversity originates and establishes during cortical development, remains largely unknown. Taking advantage of a cross-modal approach that combines in utero electroporation at different time points during cortical development, and high-throughput single-cell RNA sequencing, we identified five molecular distinct astrocyte subtypes. To understand how this molecular diversity originates, we performed trajectory inference analysis, revealing subtype specific gene dynamics during development. Moreover, these astrocyte subtypes displayed a specific cortical localization that correlates to some extend with their time of birth: early- and late-born astrocytes tend to accumulate in the lower and upper parts of the cortical column, respectively. Altogether, these results unveil a novel logic underlying the diversity of this cell population.

Predicting Treatment Outcomes in MDD using Baseline Resting-state Data: A Meta-Analysis

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Current interventions for major depressive disorder (MDD) demonstrate limited and heterogeneous efficacy, highlighting the need for improving the precision of treatment. Although findings have been mixed, resting-state functional connectivity (rsFC) at baseline shows promise as a predictive biomarker. This meta-analysis evaluates the evidence for baseline rsFC as a predictor of treatment outcomes of MDD interventions.

We included MDD literature published between 2012 and 2023 that used antidepressant, brain stimulation and psychotherapy. Pearson correlations between baseline rsFC and treatment outcomes or their equivalents were analyzed. Nodes were categorized by brain network, and pooled coefficients were generated for rsFC connections containing more than three studies.

Among the 15 included studies, pooled coefficients were generated for three types of rsFC connections: frontoparietal network (FPN) - default mode network (DMN), FPN - ventral attention network (VAN), and within DMN. The strongest predictor of treatment outcomes was the FPN-VAN, which showed a moderate to large positive effect (fixed effect model: r = 0.41 [95% CI, 0.23 – 0.59]; random effect model: r = 0.45 [95% CI, 0.13 – 0.78]). The rsFC of FPN-DMN and within DMN predicted outcomes with small to moderate effects. The rsFC in the FPN-DMN negatively predicted outcomes (fixed effect model: r = -0.17 [95% CI, -0.26 – -0.07]; random effect model: r = -0.21 [95% CI, -0.46 – 0.05]), while rsFC within the DMN positively predicted treatment outcomes (fixed effect model: r = 0.19 [95% CI, 0.07 – 0.32]; random effect model: r = 0.14 [95% CI, -0.13 – 0.41]). Heterogeneity was observed in all three types of rsFC, study design and data analysis approaches.

Despite heterogeneity in the size and direction of prediction for different rsFC connections and across different types of MDD interventions, baseline rsFC demonstrated at least a small to moderate predictive effect on treatment outcomes in depression.

Can neurofeedback on brain network interaction improve visual perception?

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Performance in visual perception tasks and recovery from visual deficits depend on spontaneous network interactions within the resting-state network associated with visual perception. Specifically, the functional connectivity (FC) in the EEG alpha band (8-12 Hz) between the brain region and the rest of the brain is likely to result in better performance in tasks that involve those brain regions.
In this study, we investigate whether participants can enhance spontaneous alpha-band rhythm interactions between visual areas and the rest of the brain. Participants received real-time auditory feedback (neurofeedback) on their FC, which enabled them to learn how to modulate their brain activity. We hypothesized that participants in the active group would enhance alpha-band FC in visual brain regions, leading to improved visual perception. This improvement would be region-specific, and therefore, such effects would not be observed in the control group. Participants in both groups underwent two days of neurofeedback training. We used two tasks before and after the neurofeedback training to quantify changes in peripheral visual perception. Preliminary results show that subjects in the active group were able to learn to increase FC in the visual areas, while FC decreased in the control group. Both groups showed improvements in visual perception, with a more pronounced improvement in the active group; however, the difference in performance between the groups was not statistically significant. This study is a step in exploring the potential of neurofeedback to enhance FC in visual areas, potentially leading to new approaches for rehabilitating visual field deficits.

Emotion components and fMRI: validating a video game paradigm testing Expectation and Uncertainty

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The generation and nature of emotions and emotional episodes continue to be subjects of active debate in the literature, but prevailing theories seem to suggest their multicomponent nature. This project aims to establish links between the multiple components of emotions and functional brain systems by developing and validating a novel procedure that actively elicits emotions in a naturalistic and dynamic manner. Drawing inspiration from appraisal models of emotion causation, we are designing an interactive, first-person perspective video game task to be experienced in virtual reality.
Our current focus is on manipulating expectation and uncertainty appraisals to link in-game events with specific emotional responses. Upon validation, the task will be integrated with fMRI to explore its effects on physiological measures such as respiration, heart rate, skin conductance, and brain activity. Here, we show that manipulating expectation and uncertainty appraisals significantly influences self-reported emotion ratings, indicating that emotional preferences are condition-dependent. These results support the multicomponent nature of emotions and align with appraisal models.

Role of ephrinb3 in POMC neurons in the control of energy balance

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Proopiomelanocortin neurons have been primarily described as controlling feeding behavior, but accumulating evidence also showed a crucial role of these neurons in the control of glucose homeostasis. For this, and in addition of being able to sense peripheral signals, POMC neurons receive direct upstream excitatory (glutamate) and inhibitory (GABA) inputs coming from a plethora of brain areas. Remarkably, EphrinBs (EphrinB1, B2, B3) proteins are well-known actor of glutamatergic synapse formation and plasticity. A study from our group showed that the modulation of EphrinB1 a during development, led to reduced number of glutamatergic inputs into POMC neurons, impaired glutamatergic-dependent activity and insulin secretion in response to hyperglycemia. EphrinBs are still expressed in POMC neurons of adult mice however we still do not know to which extend these three proteins could participate to the control of energy and glucose homeostasis through synaptic plasticity of POMC neurons. To determine the role of EphrinB3 in the control of synaptic plasticity of POMC neurons, we silenced (Pomc-Efnb3-KD) Efnb3 (gene encoding EphrinB3) in POMC neurons of male adult mice by stereotactic viral infusion and exposed the animals to high fat diet (HFD), a potent modulator of synaptic plasticity of POMC neurons. Interestingly, Pomc-Efnb3-KD male mice showed altered AMPA-dependent sEPSC of POMC neurons and displayed greater body weight gain, associated with an increased fat mass, compared to control mice. Ultimately, this project aims to provide novel mechanisms underlying the control of energy and glucose homeostasis through the synaptic plasticity of POMC neurons, and subsequently their activity.