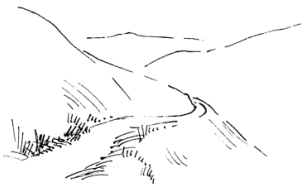
MEETING OF THE NEUROLEMAN NETWORK AND DOCTORAL SCHOOLS NLN 2022

ABSTRACT BOOK



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Barra B. as LNDS alumna will present her current work om poster board # 108

ADDICTION

Fecal Microbiota Transfer reduces alcohol preference in stressed rats

Aeschlimann L.[1],

University of Lausanne, Lausanne University Hospital (CHUV)[1]

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 (N=14), rats exposed to chronic stress during adolescence (N=25) exhibited impulsive, inattentive and disinhibited behaviors.
After 33 sessions of daily alcohol (10% weight/ volume) self-administration, all rats were screened according to the 3 criteria defined above. The large majority, 10/12, of the vulnerable group was composed of stressed rats, and most of the resilient group was composed of controls (12/14 controls identified as resilient), confirming that stress during adolescence increases the vulnerability to develop AUD-like behavior. All rats were then given access to two sources of reward: 10% w/v ethanol and saccharine (0.2 %, 0.00625 %, 0 %), two consecutive sessions for each concentration, during which stressed rats exhibited a clear-cut preference for alcohol compared to controls (2-way ANOVA, group effect ($F_{1,21}=10.73$, $p=0.0036$). 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 (and most likely gut microbiota composition).

Behavior And Neuroimaging

Trust vaccines: Introducing the trust inoculation to protect public support of governmentallymandated actions

Spampatti T.[1], Brosch T.[1], Trutnevyte E.[1], Hahnel U.[1],

University of Geneva[1]

Negative persuasive attacks and misinformation are major threats to public support of governmental mandates for pandemic and climate actions. Here, we introduce and investigate the treatment heterogeneity of the trust inoculation, first of a new kind of sociopsychological inoculation designed around the social dimensions of persuasion to protect against negative persuasive attacks and misinformation. In a preregistered study conducted with peer-reviewed preregistration, we provide evidence that inoculating citizens about the trustworthiness of key energy stakeholders moderately protected citizens' support for a renewable energy part of national energy transitions to net-zero emissions, against multiple negative persuasive attacks, in seven European countries (Austria, France, Germany, Italy, the Netherlands, Poland, and Spain; *N*=2805). Baseline trust in energy stakeholders did not moderate the effects, but the trust inoculation protected the citizens most susceptible to negative persuasive attacks, pro-environmental citizens. Our findings demonstrate that sociopsychological inoculations such as the trust inoculation are promising, easily implementable and scalable interventions to protect governmental mandates from multiple negative persuasive attacks and misinformation.

Abstract # 2

Domains of Behavior and Psychopathology Derived via Factor Analysis

Schöttner M.[1],

University of Lausanne[1]

Introduction
Predicting behavior from brain imaging data could advance the development of biomarkers for psychiatric conditions. For this, we need robust behavioral scores, combining data from questionnaires and psychological tests into meaningful summary variables.
Methods
We compared Factor Analysis (FA), Principal Component Analysis (PCA), and Independent Component Analysis (ICA) in how they decompose the Human Connectome Project's Behavioral Data to explore the latent structure of behavior and derive scores for prediction. The methods were compared in terms of model fit (variance explained), robustness (stability of factors/components over subsamples), and interpretability.
Results
PCA and ICA had slightly higher model fit than FA. FA and PCA were more robust than ICA. FA was robust for at least up to the first five factors. Using five factors/components gives a robust and meaninful decomposition with factors for Social Well-Being, Cognitive Accuracy, Psychopathology, Cognitive Speed, and Substance Use.

fMRI activations related to simple finger movement predict performance on a mental rotation task

Doganci N.[2], Iannotti G.[1], Ptak R.[1],

University Hospitals of Geneva[1], University of Geneva[2]

Functional neuroimaging suggests that the dorsal frontoparietal network (dFPN) –a system of brain regions mainly comprising the posterior parietal and superior frontal cortices –is implicated in various motor and cognitive tasks. However, it is unclear whether the dFPN serves several, computationally independent functions or is the anatomical basis of a common core function that has been reused during evolution to serve newer functions. We hypothesized that the capacity to mentally rotate images partly relies on a phylogenetically older motor process that is rooted within the dFPN. Our hypothesis predicts that neural sources involved in simple action planning may also predict performance in mental rotation. To address this hypothesis, we asked 30 healthy participants to perform a finger pressing task either when the finger was predetermined (externally-triggered) or had to be chosen by the participant (internally-triggered). Multiband fMRI was acquired in a blocked design, and activation patterns were compared across conditions. In a separate session outside the scanner, 25 of the participants who performed the finger pressing task, also performed a mental rotation task on pictures of hands or letters. In the critical comparison (internally-triggered >externally-triggered) fMRI data revealed significant activations in the dFPN and middle occipitotemporal regions. We next extracted from each significant cluster the maximum t-values and correlated these with individual reaction times on the mental rotation tasks. Maximum t-values of superior parietal lobule, dorsal premotor cortex, inferior parietal lobule, pre-SMA and ventral premotor cortex of the right hemisphere were positively correlated with the reaction times of the mental rotation of hands. By contrast, no significant correlation was found for the mental rotation of letters. Our results demonstrate that neural resources and computational processes rooted within parietal and premotor regions of the brain commonly serve simple action planning, are also relied upon when subjects mentally rotate bodily stimuli even when no overt action is produced.

Interindividual differences in brain dynamics of learning: an event-related potential topographic investigation

Raynal E.[1], Ruggeri P.[1], Brandner C.[1],

University of Lausanne[1]

Attentional processes are reported to correlate to learning, and could underlie the consistent variations reported between individuals in learning ability. However, if these processes and their related event-related potentials (ERP) vary in accordance with interindividuals differences in learning ability remain unclear. To explore this issue, we recorded electrocortical activity of forty participants during an associative learning task. Learning was assessed by the computation of signal detection index d'. Using ERP topographic analyses, we evidence i) topographic differences during early (125-150 ms) processing of the stimulus, where better learning ability covariates with a P1 coinciding component, ii) topographic differences during late (575-640 ms) stage of stimuli processing, where better learning ability covariates with a P3 coinciding component and iii) better learning ability related with higher GFP between 320-630 ms after stimulus onset. These findings suggest that better learners engage early attentional and decision-making processes more efficiently than weaker learners.

Changes in nucleus accumbens dopamine signals accompanying reward-based learning of a goal-directed sensorimotor transformation

Huang J.[1], Sandi C.[1], Petersen C.[1],

EPFL[1]

Dopamine signals are thought to be important for reward-based learning and appear to play important roles in regulating synaptic plasticity in the nucleus accumbens and the striatum. However, the precise neuronal circuit mechanisms underlying the learning of even the simplest goal-directed sensorimotor transformations remain to be precisely defined. Here, we measured dopamine signals with fiber photometry using dLight expressed in the nucleus accumbens of head-restrained mice across reward-based sensorimotor task learning. Thirsty mice were first trained in a free-licking task, during which the mouse learned to lick a spout, for which they were sometimes rewarded with water delivery. In free-licking sessions, reward triggered a positive dopamine signal, while unrewarded licks evoked a negative dopamine signal. The amplitude of the reward-triggered dopamine response decreased across most individual sessions, likely reflecting the gradual reduction in thirst across each session with accumulated reward. Subsequently, the same mice were trained over days in a whisker-detection task, in which mice learned to lick the reward spout in response to a single brief whisker deflection. Reward delivery appeared to evoke a consistent dLight response across learning days. Whisker detection task learning was accompanied by an increase in a fast sensory-evoked dopamine signal, consistent with a large body of literature indicating dopaminergic reward prediction error signals. Interestingly, dopamine signal dynamics in individual mice during the free-licking task appeared to be predictive of performance on the first day of learning of the whisker detection task. Muscimol inactivation experiments confirmed that nucleus accumbens is involved in the execution of the whisker detection task. Our results are thus consistent with a role of dopaminergic signalling in reward-based learning and further suggest that inter-individual differences in dopamine dynamics may be a predictor of future learning performance.

Cardiorespiratory fitness and sustained attention in young adults: a pre-stimulus EEG microstates investigation

Di Muccio F.[1], Ruggeri P.[1], Brandner C.[1], Barral J.[1],

University of Lausanne[1]

Previous studies suggest that cardiorespiratory fitness is positively related to sustained attention. However, the underlying brain mechanisms of this relationship remains to be elucidated. To fill this gap, we examined EEG microstates during pre-stimulus periods (2 seconds prior to stimulus apparition) in 65 young healthy individuals (18-37 years old), differing in cardiorespiratory fitness. To this aim, we first investigated the relationship between pre-stimulus microstates and response times in the PVT and then, this same relationship with cardiorespiratory fitness. Behaviorally, cardiorespiratory fitness was related to faster response times in the task. At the electrocortical level, a lower prevalence of pre-stimulus microstates A and C and a higher prevalence of microstates B, D and E was associated with faster response times. In addition, a lower prevalence of the microstates A and B as well as a higher prevalence of the microstate D was associated with higher cardiorespiratory fitness. These results suggest that the prevalence of certain microstates is associated with the efficiency of stimulus processing in the Psychomotor Vigilance Task and that high-fit individuals exhibit a typical electrocortical dynamic allowing them to allocate their attentional resources more efficiently and thus respond faster to the stimulus.

The role of afferent input in neuroprosthetic learning

Philippides A.[2], Prsa M.[1], Huber D.[2],

Université de Fribourg[1], Université de Geneve[2]

Brain-Machine-Interfaces can potentially provide powerful means to replace impaired motor functions. To improve currently available devices, it is important to gain a better understanding of the neuronal mechanisms underlying neuroprosthetic control. We have demonstrated that learning-related changes in neuronal firing can be highly specific to the conditioned neuron. These changes are likely the result of neuronal plasticity, such as long-term potentiation or more synchronous input to the conditioned neuron. Independent of the type of plasticity involved, one key question remains: what is the origin and nature of the synaptic input driving the conditioned neuron?

To identify the afferent activity driving neuroprosthetic learning, we designed a novel two-photon microscope with multiple focal planes, capable of imaging multiple cortical layers simultaneously while we condition a chosen neuron. By labeling the conditioned neurons (in L2/3) and afferent incoming axons (in L1) with spectrally different calcium indicators, this optical approach allows us to image the in- and output of specific synaptic interactions simultaneously.

Our first goal was to characterize the role of the motor thalamus (VM) and premotor areas in the learning process. Both regions show high correlations with the conditioned neuron, and with their signals we can easily reconstruct the activity patterns of conditioned neurons and its neighbors. However, calcium dynamics of buttons from the two regions also show differences. Thalamic activity is slowly evolving over a learning session suggesting a stable input contribution, which could be important for long-term memory consolidation. In contrast we observed that input from premotor areas showed more transient changes which might be related to early phases of learning. Taken togther, these experiments suggest a differential role of the two afferent input sources in the process of neuroprosthetic learning.

Awareness related visual evoked potentials vary with the cardiac and respiratory phase

Leupin V.[1], Britz J.[1],

University of Fribourg[1]

We can investigate neural correlates of consciousness by comparing the brain response to different perceptual outcomes of a stimulus presented at the sensory threshold: when it is consciously perceived, both early sensory (P1), later perceptual event-related potentials (ERPs) (VAN) and post-perceptual (LP) components are stronger than when it is not perceived. The brain is inextricably connected with the body, and cyclic variations of bodily signals, i.e. the cardiac and respiratory phase, can likewise influence perceptual awareness: baroreceptor activity during the systolic phase and its fluctuations across the breathing cycle affects the detection of simple stimuli.

To determine the relative influence of brain activity and the cardiac and respiratory phase on conscious awareness, we presented subjects with stimuli (Gabor gratings overlaid with random-dot-noise) at the sensory threshold and compared the ERPs for the same stimulus when consciously perceived with and without awareness as a function of the cardiac and respiratory phase. The P1 is modulated as a function of awareness and both the cardiac and respiratory phase: it is larger in the aware than the unaware condition in the diastolic but not the systolic phase and during inhalation but not during exhalation.

While the absence of the P1 modulation as a function of awareness in the systolic phase can be explained by concurrent baroreceptor activation, the mechanisms underlying the modulation occurring during inhalation requires further investigation.

High contextual interference practice enhances motor acuity retention and transfer in a pointing task

Cretton A.[1], Brandner C.[1], Barral J.[1],

University of Lausanne[1]

The persistence/generalization of Motor Skills Learning (MSL) is an important goal of training programs. And a bulk of evidence suggests that contextual interference (CI) modulates the effectiveness of these trainings by increasing their cognitive requirements. CI effects are well established in complex tasks involving memory and motor processes but not in simple motor acuity tasks. Therefore, 40 participants, separated into two groups, practiced during nine sessions –and four test sessions –a computer-mouse pointing task targeting motor acuity improvements. Three movement amplitudes were practiced either in random (high CI group) or blocked (low CI group) order. We found that the acquisition was delayed but the persistence/generalization (non-trained hand; new amplitudes) of the skill was better in the high compared to the low CI group. Our results highlight that increasing the cognitive demand in a pointing task is beneficial to learning and that better performance in the acquisition phase does not guarantee better learning effects.

Experience-dependent representation of sensory-, motor- and decision-related activity in primary sensory, motor, and medial prefrontal cortical areas

Oryshchuk A.[1], Sourmpis C.[1], Asri R.[1], Esmaeili V.[1], Gerstner W.[1], Petersen C.[1], Crochet S.[1],

EPFL[1]

Goal-directed behavior requires processing of incoming sensory information, making appropriate decisions, and generating relevant motor outputs. Yet, how these diverse aspects of sensorimotor transformation arise within the intricate neuronal networks of the mammalian brain remains to be precisely determined. Here, we investigated sensory, decision, and motor signals in the whisker primary somatosensory cortex (wS1), the medial prefrontal cortex (mPFC), and the tongue-jaw primary motor cortex (tjM1) in mice trained to lick for reward in response to a brief single-whisker stimulus of varying amplitude. Optogenetic inactivation demonstrated the causal involvement of all three areas during task execution. We then performed high-density extracellular recordings of neuronal firing in wS1, mPFC, and tjM1 of mice trained to associate whisker stimulus with the reward (WhiskerR+ mice). To understand task-specific neuronal representations, we also recorded in another group of mice that were exposed to the same whisker stimuli, that were not associated to reward (WhiskerR- mice). Sensory-evoked activity was almost exclusively found in wS1 in WhiskerR- mice and correlated with stimulus amplitude. In WhiskerR+ mice, sensory-evoked activity in the absence of licking (i.e. Miss trials) was also largely predominant in wS1 but a significant proportion of neurons with sensory-evoked response were also found in mPFC and tjM1. All three cortical regions were strongly modulated by licking in both WhiskerR- and WhiskerR+ mice. Only tjM1 neuronal activity was unchanged comparing spontaneous (False alarms) and whisker-evoked (Hit trials) licking in WhiskerR+ mice, suggesting prevailing coding of the licking motor output in tjM1. Finally, decision-encoding neurons - with selective activity in Hit trials, but not in Miss or False alarm trials - were found mostly in mPFC and less in wS1 and tjM1. Our results point to distinct yet inter-related roles of cortical regions for goal-directed sensorimotor transformation.

Mapping of functional connections from higher-order thalamocortical feedback circuits

Rey E.[1], Chereau R.[1], Holtmaat A.[1],

Université de Genève[1]

Projections from the higher-order of the posterior medial nucleus (POm) of the thalamus are thought to provide context-related feedback to the primary somatosensory cortex (S1). They facilitate the generation of dendritic NMDAR-dependent Ca^{2+}-events, which in turn play a critical role in sensory-evoked cortical plasticity. However, the spatial and functional relationship between POm and sensory-related inputs on pyramidal dendrites remains poorly understood. We aim at comparatively mapping POm-mediated and sensory-evoked calcium events in cortical pyramidal cell dendrites in layer 1 of mouse S1 *in vivo*. Genetically encoded Ca^{2+} sensor, GCamp7b, is expressed in pyramidal neurons in the S1 barrel field, and light-sensitive ion channel channelrhodopsin-2 (ChR2) in POm neurons. Dendritic Ca^{2+}-events in pyramidal dendrites are imaged either upon photoactivation of POm axons or upon whisker stimulation, using 2-photon-laser scanning microscopy through a cranial window.
We find that both whisker stimulation and photoactivation of the POm axons induce global, dendrite-wide Ca^{2+} events, as well as small local events that are spatially constrained to spines or similarly sized locations in the dendrites. POm photo-stimulation tends to produces proportionally less dendrite-wide and local events as compared to whisker stimulation, as well as to the combined whisker and photo-stimulation. Their local responses are also smaller in size, which is likely the result of the mono-synaptic nature of the photo-simulation-response, and more clustered, which could explain the non-linear responses to POm stimulation previously observed in the lab in electrophysiology. Furthermore, whisker-evoked local events are biased towards POm-inputs, suggesting that these inputs play a direct role in evoking sensory-related dendritic activity.

Associations between abdominal adipose tissue, reproductive span, and brain characteristics in post-menopausal women

Schindler L.[1], G. de Lange A.-M.[1],

University of Lausanne[1]

The menopause transition involves changes in oestrogens and adipose tissue distribution, which may influence female brain health post-menopause. Although increased central fat accumulation is linked to risk of metabolic diseases, adipose tissue also serves as the primary biosynthesis site of oestrogens post-menopause. It is unclear whether different types of adipose tissue play diverging roles in female brain health post-menopause, and whether this depends on lifetime oestrogen exposure, which can have lasting effects on the brain and body even after menopause. Using the UK Biobank sample, we investigated associations between brain characteristics and visceral adipose tissue (VAT) and abdominal subcutaneous adipose tissue (ASAT) in 10,251 post-menopausal females, and assessed whether the relationships varied depending on length of reproductive span (age at menarche to age at menopause).
To parse the effects of common genetic variation, we computed polygenic scores for reproductive span. The results showed that higher VAT and ASAT were both associated with higher grey and white matter brain age, and greater white matter hyperintensity load. The associations varied positively with reproductive span, indicating more prominent associations between adipose tissue and brain measures in females with a longer reproductive span. The results could not be fully explained by genetic variation or relevant confounders. Our findings indicate that associations between abdominal adipose tissue and brain health post-menopause may partly depend on individual differences in cumulative oestrogen exposure during reproductive years, emphasising the complexity of neural and endocrine ageing processes in females.

Ventral Striatal Functional Connectivity in Healthy Participants during Reward Anticipation and Links to Neurocognitive Processes

Carruzzo F.[1], Giarratana A.[2], Tobler P.[2], Kaiser S.[1], Kaliuzhna M.[1],

University of Geneva[1], University of Zürich[2]

Background
The ventral striata (VS) are strongly involved in processing reward anticipation. During reward anticipation, patients with schizophrenia show increased task-related functional connectivity (FC) between the ventral striatum and regions of the default network and the salience network. However, little is known about non-pathological FC during reward anticipation.
Objectives
This study aimed to investigate the task-related FC networks of healthy participants during reward anticipation and their link to neurocognitive processing.
Method
Eighty-four healthy participants (44 females) were recruited at the University of Zürich. All participants performed a variant of the Monetary Incentive Delay Task while undergoing event-related fMRI. The Brief Neurocognitive Assessment (BNA) was used to estimate neurocognitive levels in participants.
Results
Participants showed the expected decrease in reaction times for highly rewarded trials compared to non-rewarded trials. Whole-brain PPI analyses of the left and right VS during reward anticipation revealed FC with regions including the Mid Occipital Gyrus, Precuneus, dorsal Anterior Insula, Caudate Nucleus, Precentral Gyrus, Anterior Cingulate Cortex, Putamen, Superior Parietal Gyrus and Superior Frontal Gyrus. In addition, left VS to bilateral Anterior Insula FC negatively correlated with Symbol Coding scores.
Conclusions
These results show the different systems the ventral striata take part in, including cerebral regions that are part of the salience network, the default mode network and the visual network. Finally, these results indicate that the dorsal insula is a critical connective node for reward anticipation and strongly relates to neurocognitive levels.

Cortical circuits for context-dependent sensorimotor transformation

Ghaderi P.[1],

EPFL[1]

Flexible integration of sensory stimuli in a context-dependent manner is a key cognitive process required to generate appropriate behavior. An intriguing question, then, is how the same sensory stimulus can be interpreted differently according to context in order to generate different behavioral responses. We designed a task in which mice were trained to lick for reward in response to a brief single whisker stimulus if it was preceded by a brief Go-Tone presented one second before the whisker stimulus, but not if it was preceded by a NoGo-Tone. Optogenetic inactivation of primary whisker somatosensory cortex (wS1), secondary whisker somatosensory cortex (wS2), secondary whisker motor cortex (wM2) and anterior lateral motor cortex (ALM) during the presentation of the whisker stimulus decreased the probability of licking in the reward window. Inactivation of wM2 and ALM, but not wS1 or wS2, during the delay between the tone and the whisker stimulus reduced licking in the reward window. We investigated the neuronal correlates of context-dependent sensory processing using high-density extracellular recordings combined with high-speed video filming of facial movements. The neuronal response to the whisker stimulus in wS1 and wS2 was higher in Go-context hit trials than in NoGo-context correct rejection trials. wM2 and ALM also showed much stronger responses to whisker stimulus in the Go-context and had prominent persistent activity during the delay period following the Go-tone presentation, even in trials without anticipatory facial movements. These preliminary results point to an important role of frontal areas wM2 and ALM in context-dependent sensorimotor transformation.

Neural circuits underlying instrumental observational learning in head-fixed and freely-moving mice.

Masood A.[1],

Univeristy of Geneva[1]

Social cognition has been posited to benefit the collective success of groups. To perform better in groups, individuals must represent and integrate action-outcome for conspecifics. Neurons in the frontal cortex of socially interacting mice have been shown to represent conspecific fear[1], pain[2,3], competitive behaviour[4], and social rank[5]. However, it is still unknown if these brain circuits are involved in instrumental observational learning during goal-directed tasks. We ask this question by training mice to perform jointly in two different instrumental learning tasks. 1) We train mice to forage for reward in a head-fixed, two-alternative-forced-choice (2AFC) setting in a dynamically changing environment (two-armed bandit task)[6–8]. We then paired expert mice demonstrating the task to naïve mice to test if naïve mice follow conspecific cues and can collect more reward when they observe the demonstrating expert. 2) We developed a novel behavioral paradigm where mice were trained to perform a directional contrast discrimination task in a freely-moving 2AFC setting[9]. Mice were then paired to perform the task in a joint setting to test if mice can integrate conspecific actions to improve their decisions at times of high uncertainty. Preliminary data suggests that mice are influenced by the behavior of their conspecific with different valence depending on how reliable the choices of their partner are. Future experiments combining these behavioral tasks with optogenetic inhibition and neuronal recordings (Neuropixel probes for head-fixed, and Miniscope for freely-moving), will help uncover the neuronal underpinnings of environment and conspecific related variables in the brain.

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Visuospatial neglect is related to structural damage and disconnection caused by lesions after a stroke

Song J.[1],

University of Geneva[1]

Spatial neglect is a common post-stroke disorder that arises from brain lesions and is characterized by defects in awareness of contralesionally located stimulus (Embrechts et al., 2021; Heilman &Valenstein, 1979). It is widely agreed that spatial neglect is a heterogeneous disorder involving different clinical subtypes (Marsh &Hillis, 2008; Stone et al., 1998), such as spatial reference frames (egocentric, allocentric) (Embrechts et al., 2021; Ogourtsova et al., 2018). However, it is still unclear on the differences in brain mechanisms between different subtypes of spatial neglect after stroke. In this study, we characterized the relationship between visuospatial neglect and structural brain damage, and disconnection caused by lesions. We first calculated different structural brain indexes quantitatively representing the grey matter damage, white matter disconnection, and parcellation disconnection based on the previous brain atlas. Then, we assessed the cognitive ability of stroke patients to represent space by using several neuropsychological tests like the bell cancellation. In addition, we organized plenty of clinical cognitive tasks that measured visuospatial neglect to see how they grouped as different subtypes like egocentric and allocentric spatial reference frames. Finally, machine learning methods determined if the structural brain disconnection caused by lesions could predict different types of visuospatial deficit. Our findings suggest that different visuospatial neglect types may be related to different structural brain damage or disconnection patterns caused by lesions after stroke.

Differences in brain regions related to impulsivity are associated with variability of weight gain induced by antipsychotics

Grosu C.[3], Klauser P.[1], Alemán-Gómez Y.[2], Laaboub N.[1], Piras M.[1], Preisig M.[1], Conus P.[1], Draganski B.[1], Eap C.-B.[1],

CHUV[1], EPFL[2], UNIL[3]

Antipsychotic-induced weight gain can vary considerably among psychiatric patients. We examined the associations between weight gain and impulsivity scores and brain structures related to impulsivity (e.g. frontal lobe and striatum). Patients with early psychosis from the TIPP program in Lausanne were selected if they had brain magnetic resonance imaging data (i.e., structural and resting state functional) acquired up to one year after the start of antipsychotic medication. 19 patients (mean ±SD age: 24 ±5.0 years) with high weight gain (i.e., ≥5% from baseline weight at 1 month) and 23 patients with low weight gain (i.e., <5% from baseline weight at 1 month) were included. Analyses were repeated in a young (29 ±8.7 years, N=105) and older (56 ±6.7 years, N=875) population-based control cohort. In patients with early psychosis, weight gain was associated with higher impulsivity scores (E=1.42; 95 CI: 0.19, 2.65; *P*=0.025) and reduced gray matter volume in the frontal lobe ($P_{corrected}$=0.007). Weight gain was also positively correlated with grey matter volume in the striatum ($P_{corrected}$=0.048), and negatively correlated with the disruption in the resting state functional connectivity of frontostriatal circuits (*R*=-0.32; *P*=0.044). Among young controls, increased BMI was associated with reduced grey matter volume in the frontal lobe and increased frontostriatal connectivity. We found no association, between weight gain, frontal grey matter volume and frontostriatal connectivity in the older control group.
In conclusion, antipsychotic-induced weight gain in patients with early psychosis may be partially mediated by higher impulsivity, as shown by impulsivity scores computed from the PANSS and differences in gray matter volume and functional connectivity in impulsivity-related brain regions.

Neural Response to Psychosocial Feedback Valence in Early Adolescents

Celen Z.[1], Murray R.[1], Vuilleumier P.[1], Klauser P.[2], Merglen A.[1], Piguet C.[1],

University of Geneva[1], University of Lausanne[2]

Adolescence is maturation period that consists of many physical and psychological changes. It is a vulnerable period for mental health due to the heightened stress reactivity and protracted development of regulatory brain regions. In order to examine the response to psychosocial evaluative stress during this period, we recruited 67 adolescents between ages 13-15 and examined BOLD activity during a modified version of the Montreal Imaging Stress Task. The task consisted of sessions of an acute stressor (difficult mental calculations) followed by a positive or negative social evaluative feedback. Every session was followed by a 90 second rest period. Control sessions were easy calculations that were not evaluated, followed by a neutral feedback. Clinical variables such as trait anxiety, depression and mindfulness scores were recorded. Social feedback caused strong activation in the right anterior prefrontal cortex (aPFC), anterior cingulate cortex (ACC), bilateral anterior insula, putamen and right angular gyrus compared to control condition. During positive feedback compared to negative one, there was activation in the right middle frontal gyrus which correlated with their mindfulness scores. Region of interest analysis from activations during social feedback revealed that individuals with higher depression scores engaged the right dorsal posterior cingulate cortex (PCC) and left ACC more during negative feedback. These results show that early adolescents engage the salience network during social feedback. Negative feedback triggers midline activity relating to self-related internal focus in more depressive individuals. In conclusion, modified MIST is an effective tool to investigate the effects of psychosocial stress and shedding light on how positive feedback is processed in adolescents.

Appraisal manipulation is correlated to changes in emotion ratings and action tendencies

Tan M.[1],

University of Geneva[1]

The nature of emotions has been a topic of interest and debate. While the theory of basic emotions has had success in the scientific community, fMRI studies have shown an overlap between brain regions that are activated across different emotions. This project aims to study if appraisals are crucial to generating different emotional states, as purported in the appraisal theories. If so, we hypothesize that there should be a clearer separation in emotional states between different emotions. Building upon previous work in the lab, in this study, we manipulated two appraisals: goal obstructiveness and uncertainty. To create more immersive and naturalistic stimuli, we did these manipulations via an in-house video game. Unlike conventional stimulation methods such as pictures and movies, the interactive aspect of video games enables the execution of goal-directed actions and direct experience of their consequences, thereby evoking stronger emotions. During the experiment, we recorded participants' appraisal and emotion ratings in 40% of the trials. We also measured participants' action tendencies by logging events in the game.

We observed changes in appraisal ratings of goal obstructiveness and uncertainty between conditions of low and high levels of manipulation. Manipulations of goal obstructiveness affected the ratings of goal obstructiveness items to a larger extent than that of the uncertainty items and vice versa. We also found a significant change in ratings of disappointment, regret, satisfaction and surprise across the manipulations. To see if participants' behaviour changed according to our manipulations, we aggregated counts of several events on a trial level. We then trained classifiers to predict either the level of goal obstructiveness, the level of uncertainty or the condition based on these events. We conducted a leave-one-subject-out cross-validation and obtained above chance level F1 scores. Finally, we will conduct further analyses to include changes in physiology and brain activation, to have a holistic view of one's emotional state according to one's appraisals.

Neuronal mechanisms of visuo-tactile integration in mouse associative cortices

Guyoton M.[1], Matteucci G.[1], Favero L.[1], El-Boustani S.[1],

University of Geneva[1]

Objects are defined by physical properties that can stimulate different sensory modalities. Multisensory integration (MI) refers to the neural computations that transform signals originating from distinct sensory systems into a unified multimodal representation. However, the cortical circuits involved in producing coherent perceptual experiences of multimodal stimuli remain largely unexplored. In the mouse posterior parietal cortex, the rostrolateral area (RL) of the primary visual cortex (V1) receives direct inputs from both V1 and the primary somatosensory cortex (S1) but it is not clear if this is the siege of all visuo-tactile processing. We investigated how visuo-tactile signals are mapped in associative cortical regions and how these representations are used during goal-directed behaviours. Transgenic mice expressing fluorescent calcium indicator GCaMP6f in superficial cortical layers were implanted with a cranial window covering the left posterior hemisphere, providing a large optical access to somatosensory and visual cortical areas. Combining wide-field and two-photon calcium imaging, we recorded at both population and single-cell level in head-fixed mice during passive exposure to combinations of visuo-tactile stimuli. Calcium signals evoked by these stimulations helped to identify non-linear summations of visual and tactile responses in several cortical territories with different functional organizations. We further developed a Go/No-Go visuo-tactile discrimination paradigm where mice were trained to report perceptions of simultaneous visual and tactile stimuli while ignoring unisensory stimuli. We observed that mice exhibited frequent switches between strategies favouring specific sensory modalities during the task. These results illustrate how multiple cortical regions are involved in visuo-tactile MI and potentially support flexible visuo-tactile decision-making.

BlueBerry: Wireless optogenetic feedback in freely moving animals based on real-time behavioral tracking

Nourizonoz A.[1], Galinanes G.[1], Prévost-Solié C.[1], Thurnherr R.[1], Pellat S.[1], Huber D.[1],

University of Geneva[1]

Optogenetics has been extensively used by neuroscientists in a quest to manipulate neuronal activity in different brain areas and study their causal link to behavior. Applications widely vary from head-fixed settings, where stable optical access to the brain is necessary, to freely moving scenarios where maintaining natural sensory-motor variables are crucial. Thanks to recent technological advances in wireless communication, optogenetic stimulation devices can be controlled remotely, allowing to extend freely moving studies to multi-animal setups or complex three dimensional environments. However, the relatively high cost and the lack of open source systems has placed constraints on the current wireless optogenetic devices.

Here we present the BlueBerry, an open source, low cost (30$) multi-channel optogenetic device controlled and programmed remotely using Bluetooth Low Energy (BLE) protocol. The light and compact design (1.4gr - 11 x 15 x 6 mm) of the BlueBerry makes it an ideal candidate for real-time optogenetic application in freely roaming small animals such as mice or small primates. We illustrate the capability of the BlueBerry system combined with other open source frameworks such as EthoLoop (www.etholoop.org) for freely moving mice in two different experimental settings: 1) stimulation of the ventral tegmental area (VTA) to reinforce execution of specific type of behavior repeatedly in naturalistic 3D environments and 2) stimulation of somatosensory cortex in a “infinity-Y-maze” solving task where the mouse has to transform the artificial sensory feedbacks into navigation decisions (left or right) at every intersection.

Dynamics in stimulus-feature selectivity of VIP-expressing interneurons in the mouse primary somatosensory cortex during sensory discrimination learning

Bawa T.[1], Chéreau R.[1], Holtmaat A.[1],

University of Geneva[1]

During sensory learning, cortical networks are remodelled to encode the new information. Previously, we have shown that in this process, layer (L) 2/3 pyramidal neurons (PYRs) in mouse primary somatosensory cortex (S1) adapt their selectivity for sensory stimuli. Such response dynamics are thought to result from synaptic plasticity that ultimately increases the neurons' sensitivity to stimulus-related feedforward sensory signals. Vasoactive intestinal peptide-expressing (VIP) interneuron (IN)-mediated disinhibition of PYRs has previously been identified as an important circuit mechanism for gating the plasticity of the PYRs. They have also been found to receive long-range cortico- and thalamo-cortical feedback signals and to be activated during tactile behaviour. Here, we hypothesize that their activity is associated with behavioural outcomes, and therefore changes throughout sensory learning. To investigate this, we used *in vivo* 2PLSM calcium imaging to longitudinally monitor responses of VIP INs in S1 during a reward-based whisker-mediated texture discrimination-learning task. We found that VIP INs were activated or suppressed upon sensory touch, and a large proportion of them exhibited a significant change in their stimulus selectivity with learning. Interestingly, only a small fraction of VIP INs were selective to the textures themselves, while a large fraction reflected the behavioural outcome associated with the stimulus. Additionally, VIP IN activity was modulated by reward history, specifically during the learning phase just prior to the expert phase. Together, our work suggests that VIP INs in S1 convey sensory discrimination information to L2/3 PYRs, which may contribute to sensory perception-based shaping of PYR response selectivity and learning.

Effort mobilization and action selection in moral decision making

Monnor T.[1], Tisserand Y.[1], Rudrauf D.[1], Preuschof K.[1], Ugazio G.[1],

University of Geneva[1]

Decision-making is central to human activities and survival. Understanding of the decision-making process has been intensively studied in neuroeconomics, particularly how individuals would process and respond to financial rewards. However, it is less studied how the decision-making process would be, when it involves moral preferences, instead of financial rewards. Also, recent work has shown that different neural networks are active when processing financial and moral preferences. (Ugazio, 2011) Therefore, it is less likely that the understanding of the decision-making process in an economic setting would be fully feasible to explain the moral decision-making process. This project aims to further an understanding of the moral decision-making process by focusing on effort mobilization and behavioral responses using virtual reality. In particular, with a similar series of tasks, we will investigate differences in the subjects' physiological and behavioral responses to financial versus moral rewards. We expect to see differences in effort mobilization in the two kinds of decision-making in each individual. Also, the variation of such differences at a group level should be investigated, and explained by a varied degree of empathy across individuals.

Differential effects of motivation on probability judgements about free vs imposed choices

Salem Garcia N.[1], Massoni S.[3], Lebreton M.[2],

University of Geneva[1], University of Geneva, Paris School of Economics[2], Université de Lorraine, Université de Strasbourg[3]

Tracking uncertainty about the environment is crucial for adaptive behavior. However, people often make errors when estimating probabilities, particularly being prone to numerous affective and motivational effects. Some theories of motivated cognition propose that a general *desirability bias* affects all probability judgements equally (overestimating the probability of states of the world associated with obtaining rewards or avoiding punishments). Here we challenge this view across multiple perceptual discrimination experiments (total N = 401), where we manipulated choice agency (whether participants were faced with free choices, imposed choices, observed choices, or their own choices from previous trials) and monetary incentives (magnitude and valence of potential outcomes for correct/incorrect choice), measuring their effects on probability judgements about choices being correct. We falsify a generalized desirability bias by demonstrating a) increased probability judgements with net rather than absolute incentive value, and b) higher effects of incentives on probability judgements about self-generated actions. These results show that probability judgements are affected by a *contextual valence effect* rather than a desirability bias, and that judgements about one's own behavior are differentially affected, being more sensitive to this effect.

Chemogenetic manipulation IL projection to the VTA on impulsive action and risk-based decision-Making in RHA and RLA

Uruena G.[1], Arrondeau C.[1], Marchessaux F.[1], Ginovart N.[1],

UNIVERSITY OF GENEVE[1]

Impulsivity is a complex personality trait characterized by a predisposition to take premature actions and undue risks. Converging evidence links impulsive actions to increased dopamine (DA) release and decreased activity in the medial prefrontal cortex (mPFC). The infralimbic cortex (IL) is part of the mPFC and projects to the ventral tegmental area (VTA), where it can affect the activity of dopaminergic neurons. Whether control of the IL projection to the VTA modulates impulsivity is currently unknown. To test this, we used the Swiss sublines of Roman High (RHA) and low (RLA) avoidant rats, which respectively show high and low impulsive action. We tested the animals in the rat gambling task (rGT) and used a chemogenetic approach to acutely inhibit the IL projection to the VTA in RLAs and to activate the IL projection to the VTA in RHAs. Preliminary data confirmed that RHAs had higher impulsive action than RLAs at baseline, although they were not more risk-preferring. Interestingly, activating the IL projection to the VTA in RHAs tended to decrease impulsivity, while inhibiting the IL projection to the VTA in RLAs tended to have the opposite effect. No significant alterations of risk preference or locomotor activity occurred as a result of the chemogenic manipulation of the IL projection to the VTA. Taking together our preliminary results suggest that impulsive action but not risk preference might be modulated by the activity of IL neurons projecting to VTA.

Toward neural markers of the flow state using EEG and video game play

Nguyen A.[3], Scheltienne M.[1], Joessel F.[3], Hillyard S.[2], Bavelier D.[3],

Fondation Campus Biotech Geneva[1], University of California, San Diego[2], University of Geneva[3]

The present work aims at characterizing, using EEG, the neural bases of the state of flow, as defined by Csikszentmihalyi &Larson (2014) - a state of full immersion and of optimal performance in the ongoing activity. We induced a high versus a low flow state in each participant through two individually tailored video game play sessions. Importantly, the induced low flow state guaranteed that participants stayed on task, trying their best as in the high flow state, avoiding confounds from off-task behaviors such as boredom or frustration.

As in Castellar et al (2019), we used an auditory oddball paradigm that required participants to respond to rare auditory oddball stimuli while playing their assigned game sessions, either in a high or a low flow state. We predicted that the target oddball sounds in the high flow state would elicit slower RTs and reduced P300 amplitudes as compared to the low flow state, in accordance with the hypothesis that irrelevant events in the high flow state would receive fewer processing resources.

Here we demonstrate the feasibility of this approach showing that ERP markers of the auditory oddball, in particular the N100 and P300 components, can be recovered at the individual subject level. We discuss how data collection has been adapted to limit artifacts (head motion, jaw tension during game play), and how artifact correction has been optimized, in particular with respect to numerous eye movements. Finally, we present our planned designs to further characterize the neural bases of flow.

Adaptive training : no longer letting our brain characteristics condition our motor skill learning ?

Schipper K.[1],

University of Lausanne[1]

What is often overlooked nowadays in the study of motor skill learning is the influential importance of the conditions in which you place the learner (i.e., the practice conditions). Different practice conditions (practice scheduling, amount of feedback, motivational drive) impact how the learner will perform and eventually learn the skill ((Brady, 2004; Lee &Genovese, 1989; Robert, 1991; Salmoni et al., 1984; Wulf &Lewthwaite, 2016). But how the conditions under which the new skill is trained, impact the brain characteristics themselves is a matter that is often neglected in the motor learning literature. Conceptual cognitive models have already suggested that the continued adaptation of an optimal level of difficulty during the learning process would help promote efficient cognitive learning (Guadagnoll &Lee, 2004; Kelley, 1969; Lövdén et al., 2010).
In the prospective longitudinal study, we aim to test these cognitive theories in the motor skill learning domain and investigate whether individually adapted training changes the impact of our predetermined brain characteristics on our learning of a new motor skill.
In the first phase of this project we tested our **newly designed bimanual motor task** in a purely behavioral pilot study. The primary aim of this pilot study is to examine the feasibility of our new experimental design and to estimate subjects average grip force stability (how well the participants maintain the correct force intensity). This will enable us to set the motor task at an appropriate level of difficulty (not too easy, not too difficult) in the longitudinal study.

Computational neuroscience & techniques

Learnable latent embeddings for joint behavioral and neural analysis

Schneider S.[1], Lee J.[1], Mathis M.[1],

EPFL[1]

Mapping behavioral actions to neural activity is a fundamental goal of neuroscience. As our ability to record large neural and behavioral data increases, there is growing interest in modeling neural dynamics during adaptive behaviors to probe neural representations. In particular, neural latent embeddings can reveal underlying correlates of behavior, yet, we lack non-linear techniques that can explicitly and flexibly leverage joint behavior and neural data. Here, we fill this gap with a novel method, CEBRA, that jointly uses behavioral and neural data in a hypothesis- or discovery-driven manner to produce consistent, high-performance latent spaces. We validate its accuracy and demonstrate our tool's utility for both calcium and electrophysiology datasets, across sensory and motor tasks, and in simple or complex behaviors across species. It allows for single and multi-session datasets to be leveraged for hypothesis testing or can be used label-free. Lastly, we show that CEBRA can be used for the mapping of space, uncovering complex kinematic features, and rapid, high-accuracy decoding of natural movies from visual cortex.

Calcium-based plasticity and cell assemblies in a detailed, large-scale cortical network model in an in vivo-like state

Ecker A.[1], Egas Santander D.[1], Bolaños-Puchet S.[1], Isbister J.[1], Reimann M.[1],

EPFL[1]

The recent developments in experimental techniques have enabled simultaneous recordings of thousands of neurons. In particular, these techniques have made it possible to study the formation of functional cell assemblies. However, characterizing the evolution of synaptic connections and their plasticity within such assemblies remains challenging. To address this challenge, we developed a complementary simulation-based approach, using a detailed, large-scale cortical network model equipped with calcium-based functional plasticity of the synapses between excitatory cells. First, we detected functional cell assemblies from the stimulus-evoked spiking activity of 185’000 excitatory cells using a combination of recently published methods. Then, using algebraic topology (counting of directed simplices), we showed that the connectivity of cell assemblies is enriched with structural circuit motifs, thus linking their underlying structure to their co-firing "function". Last, by analyzing the evolution of the 320 million plastic synapses over 10 minutes of biological time, we found that strong but rare potentiation reorganized the network dynamics, while the more frequent but weaker depression kept it stable without the addition of homeostatic mechanisms. We observed significantly more potentiation in synapses between (temporally ordered) assemblies than within them, and higher than average depression in synapses within assemblies, consistent with the experimental observation that stable structures cannot be potentiated further. In summary, we predict a highly organized structural connectivity underlying functional assemblies, small but frequent weakening of within-assembly synapses and strengthening of the ones connecting assemblies to each other.

Flattening of enhanced cortical atlases opens up new possibilities for data-driven modeling and data visualization

Bolaños Puchet S.[1], Reimann M.[1],

EPFL Blue Brain Project[1]

Digital brain atlases define a hierarchy of brain regions and their locations in three-dimensional space. They provide a standard coordinate system in which diverse datasets can be integrated for visualization and analysis, and they enable building of data-driven computational models of brain regions. For atlases of the cerebral cortex, additional information is required to work effectively with its particular, layered architecture and curved geometry. Although some approaches have been employed in the literature, no usable method to produce such information has been made openly available. To fill this gap, we describe here methods to enhance a cortical atlas with three auxiliary, voxel-wise datasets: first, a field of cortical depth; second, a field of local orientations towards the cortical surface; and third, a *flat map* of the cortical volume: a two-dimensional representation with the property that each pixel maps to a sub-volume in which the layer structure is preserved, akin to a cortical column. We apply these methods to a digitized version of Paxinos &Watson's atlas for rat somatosensory cortex and to the isocortex region of the Allen Mouse CCFv3, and define metrics to assess the quality of our results. Among the many applications of the resulting flat maps to computational modeling, we show their usefulness for: decomposing the cortical volume into columns, defining a topographic mapping for white-matter connections between sub-regions, connectivity tracing in an atlas-based model of rat somatosensory cortex, and data visualization (anatomical, simulated spiking activity, etc.). We provide an open source implementation of our methods for the benefit of the community.

Defacing biases manual and automated quality assessments of structural MRI with MRIQC

Provins C.[3], Alemán-Gómez Y.[2], Cleusix M.[1], Jenni R.[1], Richiardi J.[3], Hagmann P.[3], Esteban O.[3],

Department of Psychiatry, CHUV[1], Department of Radiology & Department of Psychiatry, CHUV[2], Department of Radiology, CHUV[3]

A fundamental limitation to data-sharing of human neuroimaging is the removal of facial features, so-called defacing, to protect individuals' privacy. Not only does this process remove information that allows identification of individuals, but it also destroys information that may be valuable in downstream analysis. In this exploratory analysis, we investigated whether defacing affects manual and automatic quality assessment of T1-weighted images. Two trained human experts were asked to rate the same image non-defaced and defaced based on the MRIQC visual reports. Furthermore, image quality metrics (IQMs) were extracted using MRIQC. Bland-Altman plots revealed differences in both the manual quality ratings and the IQMs between the non-defaced and defaced images. In particular, human raters consistently perceived defaced images as having better quality. Furthermore, the defacing influence on the IQMs was shown significant using MANOVA (Multivariate analysis of variance). We thus concluded that defacing biased both manual and automatic quality assessments on this small sample. Therefore, we will pre-register and carry out a confirmatory analysis on a larger, unseen, dataset.

A Neural Model of Task Compositionality using Natural Language Instructions

Riveland R.[1],

UNIGE[1]

We present neural models of one of humans' most astonishing cognitive feats: the ability to interpret linguistic instructions in order to perform novel tasks with just a few practice trials. Models are trained on an extensive set of 50 tasks that combine cognitive skills commonly studied in the literature, such as decision-making, selective attention, time estimation, and multisensory integration. Models receive linguistic instructions embedded by transformer architectures pre-trained on natural language processing. Our best performing models can perform an unknown task with a performance of 83% correct on average based solely on linguistic instructions (i.e. 0-shot learning), and 90% after 3 learning updates. We found that the resulting neural representations capture the semantic structure of interrelated tasks even for novel tasks, allowing for the composition of practiced skills in unseen settings. Finally, we also demonstrate how this model can generate a linguistic description of a task it has identified using motor feedback, which, when communicated to another network, leads to near perfect performance (95%). To our knowledge, this is the first experimentally testable model of how language can structure sensorimotor representations to allow for task compositionality.

Single nucleus RNA sequencing suggests altered immune response pathways in microglia and astrocytes in bipolar disorder

Amossé Q.[2], Stergios T.[1], Ceyzériat K.[2], Tournier B.[1], Millet P.[1],

University Hospital of Geneva[1], University of Geneva[2]

Background: Bipolar disorder (BD) is a chronic mental disorder that affects around 2% of the global population and is a cause of considerable disability. Despite extensive research, the mechanisms underlying BD are relatively poorly understood. Several studies, mainly considering peripheral biomarkers, suggest that BD patients present a chronic inflammation. Nevertheless, whether this chronic inflammation is associated to pathophysiological mechanisms in the central nervous system (CNS) is relatively less studied. In this work, we hypothesized the presence of alterations in immune response pathways in glial cells, notably astrocytes and microglia, in the CNS of patients suffering from BD. In addition, we hypothesized that some genes associated to a genetic risk for BD through genome-wide association studies (GWAS) are modulated in those cells. In this purpose, we used single nucleus RNA sequencing (snRNAseq) to perform a large-scale investigation of the transcriptomic alterations of microglia or astrocytes in BD.
Methods: We isolated nuclei from 7 BD and 5 age-matched control cingulate cortex *post mortem* human tissue samples. Using fluorescence-activated cell sorting, we enriched our samples in microglia and astrocytes that were then processed with the 10X Genomics Chromium Controller and sequenced with Illumina Hiseq 4000. Quality control, sample integration, dimension reduction and clustering were performed with dedicated packages in R. This allowed to bioinformatically identify and isolate microglia and astrocytes. Differential gene expression (DGE) analysis was performed separately in each cell type using a zero-inflated regression analysis and a mixed-effects model. Finally, a functional enrichment analysis (FEA) was performed on the results of the DGE analysis to identify altered signaling pathways in BD.
Results: The DGE analysis found 141 genes with altered expression in astrocytes (72 upregulated and 69 downregulated genes in BD subjects, *p.adj* <0.05), and 346 genes in microglia (213 upregulated and 133 downregulated genes in BD subjects, *p.adj* <0.05). In microglia, FEA highlighted the alteration of type-I and type-II Interferon (IFN) pathways and genes implicated in phagocytosis. In astrocytes, DGE also revealed the alteration of IFN-related pathways and genes implicated in glucose metabolism. Interestingly, almost all of the 30 genes associated to GWAS loci were expressed in microglia and astrocytes. Notably, one of these genes, *ADCY2,* encoding for an isoform of the adenylate cyclase, was significantly and strongly upregulated in the astrocytes of BD subjects (*fold change* 1.76, *p.adj* = 0.0391).
Conclusion: This is, to our knowledge, the first snRNAseq study to show cell-specific transcriptomic alterations of immune response and metabolic pathways in microglial cells and astrocytes in BD. Furthermore, our results suggest that GWAS loci-associated genes map onto microglia and astrocytes and that these cells play a role in the pathophysiology of BD and may represent targets for the development of inflammation-related therapeutic approaches.
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Fitting recurrent spiking network models to study the interaction between cortical areas

Sourmpis C.[1],

EPFL[1]

We performed extracellular recordings simultaneously from the whisker primary sensory cortex (wS1) and the medial prefrontal cortex (mPFC) of mice performing a tactile detection task (Fig.1A) and then fit a recurrent spiking neural network (RSNN) to the recorded activity.
We model the recorded activity using three distinct neural populations representing (1) sensory input, (2) wS1, and (3) mPFC as illustrated in (Fig.1B). The input to the wS1 is modelled by a population of Ninput = 128 Poisson ”neurons” tuned to the whisker stimulation. Each of the two recorded areas (wS1 and mPFC) is modelled by a population of 300 conductance-based neurons where 85% (NE = 255) are excitatory, and 15% (NI = 45) are inhibitory. Within an area, every neuron can connect to every other neuron, but we assume that only excitatory neurons can project to other areas.
We assign each neuron in the model to a corresponding recorded neuron belonging to the same sub-population (same neurotransmitter and area) and define a loss function to minimize the mean squared error between the activity statistics of the recorded data and the tuned RSNN [2]. The activity statistics are the baseline firing rate of every neuron and the population-averaged peristimulus time histogram (PSTH) for each of the four sub-populations. We optimize the entire connectivity matrix (within and across areas) based on the aforementioned loss using back-propagation through time (BPTT) for spiking neural networks [3, 5] and synaptic rewiring [1] while respecting Dale’s law. After optimization, the resulting matrix provides a possible connectivity pattern (Fig.1C) that explains the recorded activity statistics in wS1 and mPFC (Fig.1D).
To validate this modelling approach, we perform a virtual ablation on the fitted model and compare the resulting activity with experimental manipulations affecting the late response component in wS1. Our model reproduces the finding that a secondary-late response of the whisker stimulation is due to feedback from higher-order cortical areas (Fig.1D) [4, 6]. Since many other areas are involved in this task in a real mouse brain, we cannot claim that we built a full model of wS1 and mPFC. However, we believe that this modelling approach can help us to understand better the activity in cortical circuits and test hypotheses concerning possible neural computations such as the importance of feedback from high-order areas to wS1.

Computational modeling of the unitary local field potential

Tharayil J.[2], Reimann M.[2], Neufeld E.[3], Schürmann F.[2], Destexhe A.[1], Markram H.[2],

CNRS[1], EPFL[2], IT'IS Foundation[3]

The local field potential (LFP) refers to the voltage recorded by electrodes placed within neural tissue. The unitary LFP refers to the contribution of a single action potential, and its downstream effects, to the LFP signal; analyzing the unitary LFP may shed light on the micro-scale origins of the LFP signal. The unitary LFP also serves as a kernel, which when convolved with spike times from a phenomenological model, reproduces the LFP signal.

Analysis of the unitary LFP in vivo has shown that the LFP primarily reflects inhibitory activity [1], but in vivo studies are limited by the difficulty of triggering action potentials in arbitrary cells, as well as uncertainty in the estimation of the unitary LFP. The unitary LFP depends on the morphology and physiology of the spiking cell and its postsynaptic targets, as well as on their positions relative to the recording electrode, and the connectivity and activity of the network. Computational modeling provides access to these parameters, allowing us to quantify their effect on the unitary LFP.

We evaluate the unitary LFP recorded from a cortical column in an in silico reconstruction of the rat somatosensory cortex, consisting of biophysically-detailed cells with realistic connectivity, based on the model in [2]. To calculate the unitary LFP from a selected cell, we run two identical simulations; for one of the two simulations, an additional synaptic input, corresponding to the action potential from the selected cell, is added. The contributions, from each cell, to the LFP from the two simulations are calculated and subtracted, yielding the contribution to the unitary LFP.

For each selected presynaptic cell, simulations are run for multiple LFP recording electrode positions. We quantify the impact of the additional action potential in terms of the amplitude and width of the difference in the extracellular potential, averaging over several trials. We identified non-trivial relationships between these metrics and the mean path length from the synapses on each postsynaptic cell to its soma, and the relative location of the efferent cell with respect to the electrode.

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Whether, how, and how well humans encode values in memory

Patel N.[1],

University of Geneva[1]

The framework of reinforcement learning has enjoyed tremendous success in the past decade, not only in achieving superhuman performance in games but also in helping model behavior in complex tasks. However, it does not take biological constraints, such as limited memory resources, into account. We had previously extended the standard RL framework to develop a normative theory of what, how, and how well should we remember things when we operate with limited memory resources. In this project, we build upon that work to design experiments to test our theory on human subjects.

3D brain imaging to predict gene therapy efficacy for neurological disorders

Duarte F.[1], Vachey G.[1], Ramosaj M.[1], Regio S.[1], Sipion M.[1], Rey M.[1], Déglon N.[1],

CHUV-UNIL[1]

The development of tools targeting specific neuronal circuits combined with refined quantitative analytic methods will facilitate the establishment of gene therapies for neurological disorders. We developed a 3D-based imaging analytic workflow to predict treatment efficacyof a novel therapeutic strategy for Huntington's disease (HD). The strategy consists in the delivery of an AAV-based KamiCas9 to inactivate the disease-causing gene (mutant huntingtin; mHTT) in the cortico-striatal neuronal network affected in HD by co-injecting AAV2/10 and AAV2retro in the striatum. Given the AAV-KamiCas9 neuronal tropism, we theoretically anticipated a maximal transduction efficiency of 65% in the striatum and 25-27% in thecortical striatal-connected areas based on data from the cortico-striatal connectome and Blue Brain Cell Atlas. While AAV2/10-mCherry extensively transduced the striatum, AAV2retro-GFP predominantly transduced cortical neurons with striatal projections. To estimate the transduction efficiency and predict therapeutic efficacy, we then co-registered 3D-imaged brains to the Allen Brain Atlas using the MIRACL algorithm. Our analysis predicted a HTT editing efficiency of 60% in the striatum and 12% in cortical transduced areas. As predicted, the AAV-KamiCas9 injection resultedin the inactivation of 57% and 11% of the HTT alleles onpunches from striatal and cortical transduced areas, respectively. Considering the maximal neuronal transduction in these regions, we inferred that HTT gene was inactivated in 87% of striatal neurons and in 42% of corticalprojecting neurons. These results not only validate our therapeutic strategy but also demonstrate the power of this 3D-based quantitative workflow to predict outcomes of gene therapy strategies for neurological disorders.

In-vivo estimation of axonal morphology features from EEG and MRI data

Oliveira R.[1], De Lucia M.[1], Lutti A.[1],

LREN - CHUV[1]

The characterization of brain microstructure in-vivo allows the study of the brain in development and disease. Previously, we presented a novel approach that combines MRI and EEG data to estimate morphological features of axons in-vivo (Oliveira, 2022).
The data includes the MRI g-ratio (West, 2016) and the axonal conduction velocity (Waxman &Bennet, 1972), the latter estimated from an EEG group measure of interhemispheric transfer time (IHTT). With our model, we estimate the distribution of axonal radius in a white matter tract and the axonal g-ratio, a measure of the thickness of the myelin sheath.
In fourteen healthy human participants, we showed that the scale parameter of the radius distribution, a measure of the number of large caliber axons, was higher for visual (0.40 µm) and motor (0.44 µm) than frontal (0.20 µm) trans-callosal tracts. These estimates, consistent with histological findings, illustrate the feasibility of estimating morphological features of axonal fibers from in-vivo data.
We expand the previous approach by using velocities estimated from subject-specific measures of IHTT rather than group-specific. We used EEG to obtain time courses of neuronal activity in the cortical occipital brain areas. IHTT was obtained as the latency difference between the activations in the two brain hemispheres. Test-retest datasets were acquired from three participants.
Across participants, IHTT from right-to-left hemisphere (17.9 ms) was lower than from left-to-right (21.12 ms), in agreement with the literature (Chaumillon, 2018). The IHTT estimates across sessions showed a moderate positive correlation (r=0.68).
Having subject-specific IHTT estimates will allow the use of the proposed model at the participant level, ultimately enabling to obtain in-vivo signatures of white matter microscopic changes.

Adaptive LDA Classifier in Brain-computer interface for decoding imagined syllables

wu s.[1], Bhadra K.[1], Marchesotti S.[1], Giraud A.-L.[2],

University of Geneva[1], University of Geneva;Institut de l'Audition Centre de l'Institut Pasteur[2]

Brain-Computer Interfaces (BCI) aim to establish a pathway between the brain and an external device without the involvement of the motor system, relying exclusively on neural signals. Our work aims at developing a BCI system that can effectively decode imagined speech units (here two syllables) directly from electroencephalography (EEG) signals. Most current EEG-BCIs decoders are based on static classifiers, whereby the classifier's parameters are computed once and are used throughout the entire experiment. This approach suffers for the intrinsic non-stationarity of EEG signals and might contribute to a poor feature separation between two classes. To address this issue, we have developed an adaptive Linear Discriminant Analysis (LDA) classifier able to extract properties of new incoming EEG signals in real-time and be updated accordingly. First, we have identified, with offline simulations based on pre-recorded data, the optimal parameters to be updated: the Update Coefficient (UC) for the mean and the covariance matrix. We then tested the effectiveness of our approach offline and observed that optimizing these parameters with which the classifiers is updated improves decoding accuracy. The improvement occurs not only when the parameters are computed separately for each individual's data, but also when applied at the group level, potentially reducing the experimental time. Further, decoding accuracy at the individual level could be improved by including incrementally data recorded during previous days of BCI-control training. These offline preliminary results will be applied in the near future to online BCI-control sessions and will provide a valuable tool to the development of an effective non-invasive speech BCI.

Characterization of cardiac noise in brain quantitative relaxometry MRI data

Raynaud Q.[2], Lutti A.[2], van Heeswijk R.[1],

Department of Diagnostic and Interventional Radiology, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland[1], Laboratory for Research in Neuroimaging, Department for Clinical Neuroscience, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland[2]

Cardiac fluctuations are a major source of noise in brain Magnetic Resonance images (MRI) and limit the sensitivity of MRI data to brain change. In this work, we develop a framework to characterize cardiac-induced noise in brain MRI data. We illustrate this framework on the analysis of quantitative maps of the MRI-derived tissue parameter R2*.

Multi-echo MRI data was acquired in-vivo on five participants, using a custom-made 3D FLASH sequence. The data was sampled continuously for 1 hour with an optimized sampling kernel. The participants' cardiac rhythm was recorded using a pulse-oximeter and the MRI data was retrospectively binned according to its phase within the cardiac cycle. Cardiac-induced noise was estimated in the native space of the MRI data ('*k-space*') by fitting changes across the cardiac cycle with Fourier series of sinusoidal functions (Tijssen, 2014). From the modeled cardiac noise, we identified the fraction of the data most sensitive to cardiac-induced noise and estimated its effect on the variability of the R2* estimates (sensitivity).

Cardiac-induced fluctuations account for 33±4% of the R2* variability in the brainstem and 38±9% in the cerebellum. The amplitude of cardiac-induced noise is one order of magnitude larger at the center of k-space. The 22% of voxels at the center alone account for 19±4% of the cardiac-induced variability in R2*.

This work lays the basis for the development of new acquisition strategies that mitigate cardiac-induced noise in brain MR images, improving the sensitivity of MRI data to brain changes in neuroscience studies.

Quantifying the impact of scanner bias on the construction of structural connectomes

Patel J.[1], Tarun A.[1], Bolton T.[1], Tourbier S.[1], Alemán-Gómez Y.[1], Schöttner M.[1], Richiardi J.[1], Hagmann P.[1],

University of Lausanne[1]

Introduction

Physical connections between pairs of regions in the brain constitute the structural connectome (SC). In the past years, extensive research has focused on SC-based analysis of the brain networks of diseased and normal populations. SC derivation involves numerous complicated steps: in particular, the nodes are created by segmenting and parcellating the T1/T2 weighted MRI scan, and the links between them are constructed by running tractography on the diffusion-weighted MR images. Up to this date, it remains a research problem of its own to derive reproducible SCs independent of the acquisition parameters of the scanner used. In order to advance research involving SC analysis, it is important to build a framework that minimizes scanner bias. However, before proceeding in that direction, the impacts of different acquisition parameters on the computed SCs must first be quantified. In this work, we thus set to evaluate the effect of scanner bias over the nodal and edge-wise properties of the SCs.

Methods

We downloaded 99 unrelated subjects from the Human Connectome Project (HCP) and synthetically generated images of different resolutions. The original images were acquired at 0.7 mm^3 anatomical resolution, 1.25 mm^3 diffusion image resolution, and multi-shell b-values of 1000, 2000, and 3000 s/mm^2. The synthetic dataset is composed of two more diffusion image resolutions of 2.0 mm^3 and 2.3 mm^3. We also evaluated each single shell b-value, yielding 3 diffusion resolutions and thus producing 9 different parameter combinations for each subject.

We used Connectome Mapper 3 to compute the SCs. Tractograms were generated with the following parameters: deterministic tractography, white matter seeded, constrained spherical deconvolution of order 8 with 2 million output streamlines. To define the individual SCs, we extracted normalized fiber density (Lausanne parcellation scale 3, 274 regions of interest).

The differences across SCs were evaluated in terms of nodal strength distribution (*i.e.*, the degree distribution of weighted SCs). Then, we quantified the distance between connectomes by vectorizing individual SCs and computing the pair-wise L1 distance between all 9 combinations of different acquisitions, thus producing a 9-by-9 distance matrix for each subject.

Conclusion

In conclusion, we observed that different acquisition parameters introduce distinct effects over the computed SCs. The jump from b-values of 2000 to b-values of 1000 has a greater impact on the results compared to the jump from b-values of 3000 to 2000. As topological changes in the SC as a result of scanner parameter changes remains to be assessed, future work could leverage tools such as Topological Data Analysis to gain further understanding as to which connections are the most affected.

Stability of point-process generalized linear models of neural activity during speech processing

Mohammadi N.[2], Giraud A.-L.[1], Proix T.[2],

Department Of Hearing Institute, Institute Pasteur Center, Paris, France[1], Department of Basic Neurosciences, Faculty of Medicine, University of Geneva, Geneva, Switzerland[2]

Microelectrode arrays allow recording neuronal activity in human during complex cognitive behavior, such as speech processing. Neuronal models can help interpreting the resulting high dimensional recordings. A specific type of discrete and flexible model, the point process generalized linear model (PPGLM), has been widely used to capture the effect of neural history dependency as well as exogenous sensory inputs on neural activity. These models can be directly fitted to neuronal recordings, but it has been shown that fitted models can sometimes generate unstable dynamics leading to non-realistic firing rates despite passing common statistical goodness-of-fit tests. Here we provide a dynamical system continuous representation of the model that can help predict the stability of the fitted model. Our results are in conformity with previous studies and explain why and under which conditions the system shows stable, bistable or unstable dynamics. We validated our results against PPGLM generated dynamics. In our next step, we will directly validate our results using PPGLM fitted on neuronal recordings during speech processing, thus opening the way for a direct analysis of underlying latent dynamics.

Development and plasticity

Shank3 knock-out mice present asynchrony in neurons controlling orienting responses and social interaction

Contestabile A.[2], Solié C.[1], Espinosa P.[2], Musardo S.[2], Bellone C.[2],

Sorbonne Université[1], University of Geneva[2]

Social interactions are highly complex behaviors composed of different sequential and parallel events. Orienting responses are one of the first and necessary steps to engage a social interaction, but the neural circuits controlling social orientation remain largely unknown. Although the Ventral Tegmental Area (VTA) has been identified as a critical substrate for social behaviors, the inputs that control this important midbrain structure during specific aspects of social interaction remain understudied. Here, we investigated the activity, function, and synchronicity of superior colliculus neurons projecting to the VTA (SC-VTA), which receive inputs directly from the retina. Fiber photometry experiment revealed that SC-VTA neurons display social interaction anticipatory calcium activity, which correlates with orienting responses towards an unfamiliar conspecific or a moving object.

Moreover, protracted phasic stimulation of the SC-VTA pathway promoted head/body movements and decreased social interaction. Since the SC-VTA pathway is implicated in orientation and patients affected by autism spectrum disorders (ASDs) often present reduced attention and social orienting response, we investigated this pathway in a *Shank3* KO mouse model. Firstly, we confirmed the deficits in the social orientation of these mice. In a second moment, we investigated the calcium signals of superior colliculus neurons projecting to VTA in *Shank3*$^{+/+}$ and *Shank3*$^{-/-}$ mice at a single-cell level. Remarkably, we observed a dramatic decrease of correlated neurons and a lack of synchronicity during orienting responses in *Shank3*$^{-/-}$ mice. These dysfunctions at the neuronal level could explain social orienting and interaction deficits.

Neural dynamics associated with learned sociability in adult Drosophila melanogaster

Lobato Rios V.[1], Ramdya P.[1],

EPFL[1]

Sociability, the ease with which individuals interact with conspecifics during E.g., collective foraging, coordinated prey avoidance, and courtship, is critical for an animal's survival. Studies in several model organisms including mice, flies (*Drosophila melanogaster*), and worms (*C. elegans*) have identified environmental factors, genes, and neural circuits whose disruption affects sociability [1,2,3]. However, the neural dynamics associated with sociability remain largely unexplored. We raised female wild-type flies in one of two social contexts: isolated or grouped. Grouped flies show sociable behaviors, including active leg-body interactions. By contrast, isolated animals showed a constellation of behaviors including social fear and avoidance. We found that these animals adapt to their neighbor and became sociable over several hours. Thus, sociability in *Drosophila melanogaster* is a learned state. Isolation dramatically alters an animal's reactions to same-sex, conspecific neighbors. We next asked which sensory cues mediate this learning. We found that learned sociability is largely multimodal: it is mediated by visual experience and exposure to conspecific odors. Finally, to uncover neural dynamics associated with this social adaptation, we recorded descending neuron populations (~100 neurons) in tethered isolated animals (female flies expressing GCaMP6f and tdTomato) exposed to a freely behaving conspecific neighbor during two-photon microscopy over the course of one hour. Our results reveal how neural population dynamics adapt through social experience and open the door to studying how sensory cues impact the formation of social memories.

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Structural plasticity in the monkey entorhinal and perirhinal cortices following selective hippocampal lesion

Villard J.[3], Chareyron L.[3], Piguet O.[3], Lambercy P.[3], Lonchampt G.[3], Banta-Lavenex P.[1], Amaral D.[2], Lavenex P.[3],

UniDistance Suisse[1], University of California at Davis[2], University of Lausanne[3]

Populations of immature NeuN-positive neurons expressing the anti-apoptosis Bcl-2 marker are present in several regions of the adult mammalian brain, including the amygdala, and the entorhinal and perirhinal cortices. The functional role of these immature neurons is currently unknown, but we have previously shown that neonatal and adult hippocampal lesions increase the differentiation of immature neurons in the monkey amygdala. Here, we aimed to determine whether similar changes occur in the entorhinal and perirhinal cortices following hippocampal lesion in the same animals. We performed design-based stereological analyses of Nissl-stained and Bcl2-stained sections to estimate the number and soma size of immature and mature neurons in different subdivisions of the entorhinal and perirhinal cortices. We found different lesioned-induced structural changes in the entorhinal and perirhinal cortices that were further influenced by the time of the lesion. Following neonatal hippocampal lesion, the number of immature neurons was generally higher in the entorhinal and perirhinal cortices, as compared to control and adult-lesioned monkeys. The number of mature neurons was higher in layer III of area Er of the entorhinal cortex, but it did not differ from controls in layer II of area 36 of the perirhinal cortex. Following adult hippocampal lesion, the number of immature neurons was lower in the entorhinal cortex but it did not differ from controls in the perirhinal cortex. The number of small mature neurons was lower in layer II of area 36, but it did not differ from controls in layer III of Er. Consistent with prior findings in the amygdala, hippocampal damage may have influenced neuroblast migration and the differentiation of immature neurons in a subdivision-specific manner in the entorhinal and perirhinal cortices. Such lesion-induced neuronal plasticity sheds light on potential mechanisms that may facilitate or limit functional recovery following focal brain injury in an age-dependent manner.

Loss of MCT4 in microglia results in altered brain development and anxiety-like behavior

Monsorno K.[2], Buckinx A.[2], Ginggen K.[2], Lalive A.[2], Tchenio A.[2], Benson S.[1], Vendrell M.[1], Pellerin L.[3], Mameli M.[2], Paolicelli R.[2],

University of Edinburgh[1], University of Lausanne[2], Université de Poitiers[3]

Microglia, the tissue-resident macrophages of the central nervous system, actively participate in brain development by supporting neuronal maturation and refining synaptic connections. Accumulating evidence points towards the involvement of differential substrates catabolism in the regulation of immune cells, including microglia. In particular, lactate, which sustains brain energetics and synaptic activity, also dictates responses of peripheral immune cells. However, the physiological role for lactate in modulating microglial function is still largely unexplored. In our study, we found that upon lactate exposure microglia upregulate the expression of the monocarboxylate transporter 4 (MCT4), which is involved in lactate exchange. Exogenously given lactate is readily shuttled into primary microglia and this correlates with an increase in lysosomal acidification. In order to assess the significance of lactate transport in microglia *in vivo*, we generated and characterized a microglia-specific conditional knock out (cKO) mouse model for MCT4. Two weeks-old cKO mice present alterations in hippocampal microglial density and in CD68+ phagolysosomal structures. This is associated with increased levels of synaptic markers in the hippocampus, altered excitatory post-synaptic currents as well as an enhanced susceptibility to develop kainic acid-induced seizures. Additionally, adult cKO mice display an anxiety-like phenotype. In summary, this study highlights the importance of microglial MCT4 for brain circuitries development and function. Given the established role of microglia in neuropathology, a mechanistic understanding of lactate-dependent microglial modulation may be relevant for targeting microglia in brain diseases.

Cell type-specific plasticity of cortical neuron fate

Fièvre S.[2], Morassut I.[2], Baumann N.[2], Bartolini G.[1], Klingler E.[2], Jabaudon D.[2],

CHUV Lausanne[1], University of Geneva[2]

Cell type specification is a dynamic developmental process, crucial for the establishment of proper brain circuits. Till now, the extent to which intrinsic genetic programs and extrinsic mechanisms contribute to the acquisition of individual cellular identity and connectivity remains poorly understood. Focusing on the development of the stereotyped circuit of the rodent primary somatosensory cortex (S1), we assessed how the identity, electrophysiology and connectivity of diverse cell types is affected by environmental changes. To systematically assess to which extent the acquisition of cellular identity is modulated by input/activity-dependent components, we profiled the developmental trajectories *in vivo* and compared them with *in vitro* models, deprived of their endogenous environment. Using high-throughput single nucleus RNA sequencing and deep neuronal network-based machine learning classification, we unbiasedly assigned the molecular identity of the different cell types and revealed that layer 4 cortical neurons are the most environment-sensitive. Moreover, this is further supported by functional data showing that layer 4-specific connectivity features are not recapitulated *in vitro*. Our study reveals a cell-type specific predisposition to environmental modulation during fate acquisition in the developing mammalian cortex.

Area-specific abnormal development of cortical circuit in a 22q11 deletion mouse model

Balavoine E.[2], Olusakin J.[3], Limoni G.[1], Klingler E.[2], Jabaudon D.[2],

EPFL[1], University of Geneva[2], University of Maryland School of Medecine[3]

DiGeorge syndrome (or 22q11 deletion syndrome) is a human developmental disorder caused by a 1.5 to 3.0 MB microdeletion on chromosome 22 characterized by cardiovascular and craniofacial malformations and cognitive impairment. It is the genetic neurodevelopmental disorder with the highest association with schizophrenia, making it an interesting condition to identify genes underlying neuropsychiatric disorders. “LgDel” mice have a microdeletion of chromosome 16, which recapitulates the human chromosomic deletion as most gene homologs are located in one portion of this chromosome; little is known about the impact of the deletion on distinct cell types and distinct brain regions during circuit development. Here, we investigated the transcriptional trajectories of distinct cortical cell types in wild-type and LgDel mice during postnatal development using single-cell RNA sequencing in various cortical areas. Our results suggest cell-type and area-specific anomalies that may contribute to behavioural phenotypes of this disorder.

Effect of a peptide secreted by astrocytes on hippocampal adult neurogenesis

Carron C.[1],

CHUV-UNIL[1]

Adult hippocampal neurogenesis is regulated by the neurogenic niche, which provides a structural and molecular environment enabling adult neurogenesis. In the niche, astrocytes play a predominant role, by participating to the regulation of multiple steps of adult neurogenesis, from adult neural stem cell (aNSCs) proliferation and differentiation to the functional integration of new neurons.

In this study, we used a combination of *in vitro* approaches, biochemistry and mass spectrometry to identify a peptide released by astrocytes that regulate adult neurogenesis. The secreted peptide, named peptide P9, is derived from the phosphoprotein enriched in astrocyte protein (PEA15) which is a cytoplasmic protein involved in the regulation of proliferation and apoptosis. Using live-cell imaging, we found that P9 increased the proliferation and reduced cell death of aNSCs. *In vivo*, P9 increased cell proliferation in the dentate gyrus, resulting in increased net hippocampal neurogenesis. We next used immunoprecipitation and transcriptomics to define the molecular pathways involved in the effects of P9 on cell proliferation.

These results indicate that astrocytes release peptides that regulate hippocampal neurogenesis in the adult brain. Since astrocytes are regulated by neuronal activity, this mechanism may contribute to an on-demand addition of new neurons in the hippocampus. Furthermore, understanding the mechanism of action of the astrocyte-secreted peptide P9 on adult neurogenesis in the hippocampus could be an interesting therapeutic strategy to stimulate adult neurogenesis in pathological conditions.

Executive Functions Assessment in Very-preterm Children at School Age: A Clinical and Experimental Battery

Décaillet M.[2], Denervaud S.[1], Huguenin-Virchaux C.[1], Besuchet L.[1], Bickle Graz M.[1], Fischer C.[1], Schneider J.[1],

CHUV[1], University of Lausanne/CHUV[2]

While the survival rate of very-preterm children has increased in the last decades, they are still at risk to develop long-term neurodevelopmental impairments, especially regarding their self-regulatory and executive abilities. These skills rely on executive functions (EFs), an umbrella term encompassing the core capacities for inhibition, shifting, and memorizing. Comprehensive batteries exist but are time-consuming and therefore not suitable for all pediatric neuropsychological assessments. The Flanker task is an experimental computer-based task that has the advantage to last less than ten minutes while giving multiple EF measures.

Thirty-one very-preterm children aged 8-10 years benefited from a follow-up visit including a standardized EFs assessment and a child-friendly version of the Flanker task.

First, we found that very preterm children performed in the high norm for most clinical tests (i.e., WISC-V, BRIEF, and NEPSY) except for the CPT-3 where they were slower and made more omission errors, which could indicate inattentiveness. Second, the Flanker task scores were correlated with the clinical testing. Finally, in line with previous results, compared to control term children, very-preterm children had poorer performance in the global EF measure and showed a lower accuracy.

These findings first suggest that very-preterm schoolchildren globally display normal intelligence. However, subtle difficulties that appear to relate to EFs are observed. This child-friendly version of the Flanker Task has demonstrated a good sensitivity in capturing executive functioning with good discrimination of mild difficulties and thus could be used instead of the clinical tests during the neuropsychological assessments or be suitable as a screening test.

Keywords: very preterm birth, executive functions, neuropsychological tests, cognitive development

The role of Neurod2 in the development of cerebellar GABAergic interneurons

Xiong B.[2], Mazaré N.[2], Runge K.[1], de Chevigny A.[1], Telley L.[2],

Aix-Marseille University[1], University of Lausanne[2]

In the cerebellar cortex, GABAergic interneurons have an important role in regulating Purkinje cell output. They derive from PAX2 progenitors and specify into diverse mature interneurons in different layers of the cerebellar cortex. Previous research has shown that mice lacking Neurod2, a bHLH transcriptional factor, show significant developmental defects and depletion of a subset of GABAergic interneurons, suggesting a potential role of Neurod2 in the specification of cerebellar GABAergic interneurons. However, how it is involved in their specification trajectory remains unclear. To investigate the role of Neurod2 in determining the specification of GABAergic interneurons in the cerebellar cortex, we combine immunofluorescence approaches to assess the development of the interneuron with single nuclei RNA sequencing technology to investigate the molecular differences in interneurons between wild-type and Neurod2$^{-/-}$ mutant mice. We first observe the absence of basket cells and stellate cells (Parvalbumin+) and significantly increased PAX2+ cell population in the molecular layer in mutant mice from adolescence to adulthood. Interestingly, PAX2+ cells in adult mutant mice express markers of Golgi cells that are normally distributed in the granule cell layer in the wild-type, indicating that these PAX2+ cells are no longer immature but develop in a different trajectory and probably contribute to the maintenance of GABAergic synapses in the molecular layer. Single-nuclei RNA-seq from wild-type and mutant conditions from P0 to P35 confirmed our observation. Together, our findings suggest that Neurod2 is necessary for the development of GABAergic interneurons and plays a role in determining their laminar position of in the cerebellum.

Towards the spatial atlas of cell populations in the developing mouse brain

Khven I.[1], La Manno G.[1],

EPFL[1]

The development of single-cell RNA sequencing (scRNAseq) techniques made a revolution in our understanding of the cellular complexity of the tissues. Recently more than 900 transcriptionally distinct cell states were identified in the developing mouse brain (La Manno, et al 2021), defining broad cell types like neuroepithelial cells, radial glia, neurons and glia more precisely. However, the tissue is dissociated in scRNAseq protocols, which leads to the loss of spatial information and hinders the possibility of computational modelling of population development. Using Hybridization-based In Situ Sequencing technique, we have located the expression of 200 marker genes in the developing mouse brain at the key developmental timepoints: E9.5 (the formation of brain vesicles), E12.5 (the peak of neurogenesis) and E14.5 (the start of gliogenesis). Relevant cell states defined in scRNAseq atlas were mapped to the tissue sections. This mapping allowed us to analyze the positions of cell states relative to each other. Radial glia and radial glia-like cell states tend to occupy specific positions in the germination centers of the developing brain. Using transgenic mouse strains Foxg1^{Cre}Smo$^{-/lox}$ and En1^{Cre}Smo$^{-/lox}$, in which *Smo* gene is knocked out from forebrain or midbrain respectively, we have identified the populations of progenitor cells that are affected the most by the absence of Sonic hedgehog signaling. In the future, we plan to analyze the dynamic relationships of cell populations across the timeline of brain development, as well as compare these dynamics between normal and perturbed conditions.

The effect of oxytocin on microglial reactivity in a mouse model of neonatal neuroinflammation

Knoop M.[1], Possovre M.-L.[1], Jacquens A.[1], Baud O.[1],

University of Geneva[1]

Neonatal inflammation is a condition that can occur in response to prenatal, antenatal and postnatal complications. This is particularly prevalent in infants born preterm and with intra-uterine growth restriction, which occurs in about 15 million and 30 million births per year, respectively. Neonatal inflammation can lead to severe developmental consequences including behavioral disorders such as autism spectrum disorder, learning disabilities and cerebral palsy.

An important factor in the regulation of neuroinflammation are microglia, the brain's resident immune cells. Finding ways to modulate and stabilize the active microglial phenotype back to its resting state is a key objective for disease treatment, to reduce the detrimental impact on neonatal brain development.

One potential protective factor that has been identified is the neuropeptide oxytocin, as it has shown to modulate microglial inflammatory cytokine secretion. Indeed, oxytocin was found to possess neuroprotective properties in adult neuroinflammatory states and in a rat model of intra-uterine growth restriction. However, the mechanisms of effect continue to elude. In the current study, we assessed the neuroprotective potency of oxytocin cells on microglial activity in a mouse model of neonatal neuroinflammation.

We used a model of twice-daily Interleukin-1-β injections between P1 and P5 to induce neonatal inflammation. To modulate the activity of oxytocin neurons during this period of inflammatory challenge, we generated transgenic lines that express inhibitor (hM4Di) or activator (hM3Dq) DREADDs in oxytocin cells under the temporal control of daily clozapine-n-oxide (CNO) injections between P1 and P5.

We found that our model of early-life systemic inflammation in B6J mice mimics long-term clinical symptoms seen in patients. Specifically, we identified a transcriptomic upregulation of pro-inflammatory pathways in P3 microglial cells, a delay in white matter development, as well as deficits in social and cognitive behavior at juvenile and adult age. Furthermore, preliminary results support that chemogenetic modulation of oxytocin neurons could have a substantial effect on microglial morphology and transcriptomic activity, behavioral read-outs, and structural brain connectivity in our inflammation model. In this, increased activity of oxytocin neurons shows a potential protective effect in the context of inflammation, whereas silencing of these cells shows an aggravation of the inflammatory phenotype.

Our results support the regulatory abilities of oxytocin neurons in neonatal neuroinflammation, with cause for a potential neuroprotective function. Future studies are directed towards unraveling the mechanism of effect between microglia and oxytocin cells.

Morphological Characterisation of Synapses from Long-Range Connections in L1 of Somatosensory Cortex

Lee K.-S.[2], Dubois A.[1], Blanc J.[1], Knott G.[1], Holtmaat A.[2],

EPFL[1], University of Geneva[2]

Sensory perception depends on neocortical computations that integrate sensory signals with information representing internal states and environmental contexts. Neocortical layer 1 (L1) contains the main inputs that provide context-dependent "top-down" information. At the cellular level, top-down inputs, such as those from higher-order thalamocortical (TC) or long-range cortico-cortical (CC) projections, are thought to modulate activity evoked by bottom-up sensory inputs. It is unclear what distinct attributes of top-down synaptic inputs render them modulatory in nature. Here, we aim at characterizing the ultrastructural synaptic morphology of TC projections from the posteromedial nucleus (POm) and of CC projections from primary motor cortex (M1) to L1 of the primary somatosensory cortex (S1) in mice. To this end we conditionally expressed eGFP or mRuby:GCamp6s in axons from Pom or M1. Using 2-photon laser scanning microscopy, we repeatedly imaged both POm and M1 axons over several days through a cranial window. Mice were perfused and their brains tangentially sectioned. Previously imaged axons were re-identified and selected for correlative serial block-face scanning electron microscopy (SBF-SEM). In a subset of mice, we co-expressed a mitochondria-targeted peroxidase (COX4-dAPEX2), which allows high-contrast labelling of those axons post-fixation. From *in vivo* images, we are extracting and comparing various morphological properties (inter-varicosities distances, varicosity sizes, turnover, and correlations thereof). Using correlative light and electron microscopy (CLEM), we are validating these parameters, and determining various ultrastructural properties (number of transmitter vesicles, types of organelles, differences in synaptic locations, and post-synaptic features). Thus far, we have detected minor differences in some parameters. The datasets are currently being expanded to increase statistical power, and ultra-structural analysis is ongoing.

The role of fatty acid beta-oxidation in human brain development

Sudria Lopez D.[1], Knobloch M.[1],

University of Lausanne[1]

Neural stem cells (NSCs) are the stem cells that give rise to the entire brain and even continue to form new neurons throughout life. Understanding what regulates NSC behavior is thus important both for development and for adulthood. Recently, metabolism has been shown to have an important role in the regulation of stem cell activity/fate in different tissues. Previously, Knobloch and colleagues specifically described the importance of lipid metabolism for NSC quiescence, proliferation and integration of their progeny in the mouse brain. However, whether lipid metabolism plays a similar role in the regulation of human NSCs remains poorly understood.

Therefore, in this study we aim to assess the importance of lipid metabolism on human NSCs and during human brain development.

To do so, we are targeting carnitine palmitoyl transferase 1a (CPT1A), the rate-limiting enzyme of fatty acid beta-oxidation (FAO; lipid catabolism) using the pharmacological FAO inhibitor etomoxir and shRNA's against *CPT1A* mRNA. We are using monocultures of *in vitro* derived humans NSCs to assess the intrinsic effect of FAO blockage in NSC proliferation, apoptosis and differentiation capacities. To better understand the effect of FAO inhibition during brain development, we are also using cerebral organoids, which model early brain development

Our preliminary results show that CPT1A is highly expressed in NSCs during brain development. While blocking FAO in human NSC monocultures only showed subtle effects, blocking FAO in cerebral organoids strongly reduced NSC proliferations and increased cell death, suggesting that FAO is indeed an important metabolic pathway for human NSCs.

Possible roles of amyloid-β in microglia-mediated synapse remodeling

Ginggen K.[1], Monsorno K.[1], Donnelly C.[1], Place N.[1], Paolicelli R.[1],

UNIL[1]

Microglia are critical players in neuronal plasticity and function. They are dynamic, surveilling and interacting with neighboring cells and synapses. Experimental evidence shows that close contacts with synapses are driven by synaptic activity and are important for microglia-mediated synapse remodeling. Literature shows a link between synaptic activity and Aβ. Aβ has been widely studied in AD, being the major component of the extracellular plaques associated with the pathology. Interestingly, intracellular Aβ also correlates with synaptic function. Our data, supportive of high Aβ levels in the postnatal brain, led us to hypothesize that intrasynaptic Aβ might play a role in microglia-mediated synapse remodeling. Using the ArcAβ mouse model and a pharmacological approach to modulate intraneuronal Aβ level, we analyze the involvement of Aβ in microglial synaptic pruning during brain development. First, we characterized the lipidomic profiles of synaptosomes isolated from ArcAβ pups (P15), identifying candidate molecules that could promote synaptic engulfment by microglia. We found that the synaptic profile in the ArcAβ hippocampus displayed alterations in pre- and post-synaptic markers already at early time points (P15-P30). To further study the status of hippocampal synapses at P15 in the presence of mutated hAPP overexpression, we assessed mitochondrial respiration in freshly prepared synaptosomes and observed changes in respiratory capacities. Furthermore, microglial density at P15 was reduced, indicating that Aβ/hAPP overexpression is associated with early changes in microglia. Overall, these findings suggest that synaptic and microglial alterations are present at early stages in an AD mouse model, likely contributing to neurodegeneration later in life.

The circuit basis of social valence

Espinosa P.[1],

UNIGE[1]

To decide whether to approach or avoid a conspecific,individuals need first to recognize the possibly positive (appetitive) or negative (aversive) valence of the stimulus and learn this association. The Nucleus Accumbens (NAc) is a key brain region of the mesocorticolimbic circuits for evaluating valence. However, how valence is codified at the synaptic level in a social context is still an open question.

Within the NAc, D1 receptor-containing Medium Spiny Neurons (MSNs) have been related to rewarding and motivational aspects of social behavior. Using a free social interaction paradigm and calcium imaging techniques, we demonstrated that D1-MSNs respond to positive and negative social valence stimuli. Using anatomical tracing and in vitro electrophysiological recordings, we found D1-MSN strongly connected with glutamatergic neurons from the Anterior Insular Cortex (AIC) that also express D1Rs revealing a novel D1R-D1R top-down circuit between AIC and NAc. A dayafter social interaction, we evaluated glutamatergic synaptic parameters and found a dichotomous, long-term valence-dependent synaptic plasticity that occursspecifically in these neurons. Interestingly, these forms of plasticity are triggered by different firing frequencies from AIC inputs. Specifically, we showed that low-frequency stimulation drives positive valence-like plasticity, whereas high-frequency stimulation induces negative valence-like plasticity. By recruiting the same D1R positive neurons within the AIC-NAc circuit, we demonstrated long-term synaptic plasticity signatures of social valence tuned by firing frequency.

Neuroprosthesis to restore urodynamic function after spinal cord injury

MAHE L.[1],

University of Lausanne[1]

A spinal cord injury (SCI) scatters the communication between supraspinal centers and the spinal cord circuitry responsible for maintaining urodynamic functions. This loss of communication disrupts the coordination of detrusor muscle contractions and the necessary relaxation of the external urethral sphincter. Consequently, people with SCI experience constant incontinence, chronic urine retention, recurrent urinary tract infections, and other uro-renal
complications. Here, we developed a conceptual and engineering framework to design an electrical spinal cord neuroprosthesis that targets circuitry in the spinal cord responsible formodulating the detrusor muscle and the external urethral sphincter. We first established arodent model of chronic urodynamic dysfunction after SCI. Clinically-inspired assessments ofurodynamic functions revealed a complete impairment of normal micturition and significant
bladder overactivity that developed over time after injury. To identify the spinal segments mostcapable of modulating detrusor and external urethral sphincter contractions, we applied epiduralelectrical stimulation (EES) to each spinal segment, while measuring the activity of bothmuscles. We identified highlyspecific hotspots over the lumbosacral spinal cord that, when stimulated with EES, enable contraction or relaxation of the detrusor and external urethral sphincter. Chemogenetic experiments revealed that EES induces detrusor contractions through a circuitry involving large-diameter parvalbumin neurons located in the dorsal root ganglia and excitatory interneurons within the urodynamic hotspots. We then combined CT scans, MRI sequences, and computational modelling to design a neuroprosthesis that targets urodynamic hotspots in the spinal cord. This neuroprosthesis was fabricated using e-dura technology. Closed-loop algorithms adapted the onset and amplitude of EES bursts to restore the coordination between bladder contraction and sphincter relaxation. The restoration of this coordination reduced bladder hyperreflexia and triggered micturition. Future work will aim to provide a foundation to develop a neuroprosthesis to manage bladder dysfunction in people with SCI.

Development of the piriform cortex in olfaction

Ferreira c.[1],

Geneve University [1]

The cerebral cortex is composed of distinct neuronal types which assemble during development to form circuits that enable major sensory, motor and cognitive functions. In mammals, somatosensory, visual and auditory signals are processed in the 6-layered neocortex, while olfactory signals are processed in a separate, evolutionarily conserved structure, the 3-layered piriform cortex (PC). While the neurogenesis and cellular diversity of the neocortex have been extensively studied, little information is available on the development and cellular composition of the piriform cortex. In this project, we therefore focused on the development of the 3 layers of the PC during the postnatal period. We aim to establish the temporal dynamics of the generation of neurons in the postnatal piriform cortex, using single-nucleus RNA sequencing alongside with the characterization of the electrophysiological properties of the neurons of the PC.
We show that the neurons of the different layers of the PC acquire over time diverse molecular and electrophysiological signatures.

The continuum of attention dysfunction: evidence from dynamic functional network connectivity analysis in neurotypical adolescents

Rafi H.[2], Delavari F.[2], Perroud N.[1], Derome M.[2], Debbané M.[2],

University Hospital Geneva[1], University of Geneva[2]

The question of whether attention-related disorders such as attention-deficit/hyperactivity disorder (ADHD) are best understood as clinical categories or as extreme ends of a spectrum is an ongoing debate. Assessing individuals with varying degrees of attention problems and utilizing novel methodologies to assess relationships between attention and brain activity may provide key information to support the spectrum hypothesis. We scanned 91 neurotypical adolescents during rest using functional magnetic resonance imaging. We conducted static and dynamic functional network connectivity (FNC) analysis and correlated findings to behavioral metrics of ADHD, attention problems, and impulsivity. We found that dynamic FNC analysis detects significant differences in large-scale neural connectivity as a function of individual differences in attention and impulsivity that are obscured in static analysis. We show ADHD manifestations and attention problems are associated with diminished Salience Network-centered FNC and that ADHD manifestations and impulsivity are associated with prolonged periods of dynamically hyperconnected states. Importantly, our meta-analysis results reveal a relationship between ADHD manifestations and exhibiting variable and volatile dynamic behavior such as changing meta-states more often and traveling over a greater dynamic range. These findings in non-clinical adolescents provide preliminary evidence for a spectrum approach towards attention disorders.

Role of SHIP1 as a modulator of microglial function

Matera A.[1], Paolicelli R.[1],

University of Lausanne[1]

Microglia, the innate immune cells of the central nervous system, play crucial roles in brain development, plasticity and repair. GWAS studies reveal that hundreds of genetic variants associated with neurodegeneration are found in genes expressed in microglia. However, the exact function of these genes, and their roles during brain development, is poorly studied. Here, we investigated how SHIP1 influences key microglial properties. SHIP1, encoded by Inpp5d, is responsible for the dephosphorylation of $PI(3,4,5)P_3$ to $PI(3,4)P_2$, involved in actin remodeling and phagocytosis. It is predominantly expressed by microglia, and it is upregulated in the proximity of Alzheimer's plaques. Protein assessment in the wild-type mouse brain revealed high expression at P7 and progressive decrease with aging, supporting a role for SHIP1 in the early postnatal brain. Thus, we induced microglial specific conditional KO (cKO) at P3-P4, to examine consequent microglial dysfunction and potential effects on brain development. Combining confocal microscopy and 3D reconstruction, we found that microglia lacking SHIP1 are smaller in size and less complex than controls. Proteomic analysis revealed a significant increase in C1q, a well-known eat-me signal, in the hippocampus of cKO mice, which we found to be associated with decreased post-synaptic markers, PSD95 and Gephyrin. cKO mice also displayed reduced levels of MBP and decreased number of Olig2+ cells, indicating alterations in myelination. Our i*n vitro* data support an aberrant phagocytic phenotype of SHIP1 KO microglia, which engulfed and degraded higher amount of amyloid beta and synaptosomal cargoes.
Overall, this study shows that microglial SHIP1 is required for proper brain development, suggesting that risk variants in this gene might contribute to neurodegeneration by providing early susceptibility.

Controlling a brain-computer interface to decode internally spoken syllables

Bhadra K.[1],

University of Geneva[1]

Real-time decoding of covert speech from Electroencephalography (EEG) could provide non-invasive solutions for people with compromised speech, such as patients affected by aphasia. We designed an EEG-based Brain-Computer Interface (BCI) to classify two syllables having different articulatory and phonetic features. In order to investigate whether operating a BCI can be learnt, participants were trained to control the BCI daily for 5 consecutive days. We used a random forest classifier based on power spectrum density between 1-70Hz to 'train' (offline, i.e. without any feedback) and then to 'test' (online) the data with real-time visual feedback. Results show that the gamma band (30-70Hz) from the bilateral temporal electrodes largely contribute to the offline classification accuracy. Further, participants show maximum control during online BCI training on day-4, through a progressive performance improvement from day-1, followed by a decrease on day-5. Corresponding neural data showed a significant power increase on day-4 compared to day-1 in left and fronto-temporal electrodes in theta, beta, and high-gamma bands that might underpin the acquisition of BCI-control skills. EEG response related to covert speech indicate Event-Related Desynchronization and Synchronization in the frequency bands related to overt speech, namely theta, beta, and gamma bands. The location and power difference in the neural data corresponding to the two class of syllables support the classifier preference of using gamma band to distinguish between the two class of syllable. Overall, our results indicate that EEG gamma band power is effective in classifying syllable imagery and that training can improve BCI performance.

Language

Language aptitude: behavioural and neural structural correlates

Balboni I.[1],

University of fribourg and University of geneva[1]

Language aptitude has been defined as the cognitive abilities predictive of foreign language learning potential. The three main aptitude subskills, according to the traditional framework, are phonetic coding, language analytic, and rote learning abilities. More recently, the role of general cognition in language learning attainment has been recognised, for example with extensive research on the contribution of working memory to language aptitude. This new interest in the role of general cognition coincides with a growing body of literature that explores the link between language learning skills and neural measures. For example, brain structural differences have been shown in relation to phonetic production abilities, phonetic perception and discrimination, morphosyntactic skills, and vocabulary learning and size.

The aim of this work was to explore possible behavioural associations and/or dissociations between general cognitive skills, domain specific non-linguistic skills, and language skills. Moreover, we explored the relationship between individual differences in neuroanatomy and performance on tasks taping into the three above-mentioned main classic language aptitude dimensions, to investigate potential associations and dissociations across tasks in regional variation in brain anatomy.

Participants were 66 right-handed adults between 20 and 43 years of age (M= 26.06, SD=5,01). They were all raised monolingual and started acquiring their L2 between 8 and 12 years of age.

Behavioural and questionnaire measures of working memory, foreign speech imitation, musicality, verbal and nonverbal IQ, number of languages spoken, and L2 proficiency were collected for each participant. Language aptitude skills were assessed using 3 subtests of the Modern Language Aptitude Test (MLAT) measuring phonetic coding, rote learning and grammatical sensitivity. For all participants, T1-weighted structural magnetic MRI (1,5 Tesla) were also acquired.

An exploratory factor analysis (EFA) of the behavioural scores was performed to investigate possible associations and dissociations between general cognitive skills, domain specific non-linguistic skills, and language skills. Brain structural data were processed using Freesurfer (7.2) and a univariate whole-brain GLM model for each of three the traditional behavioural aptitude scores was used to uncover potential relationships with brain volume and thickness.

The EFA resulted in one main factor comprising language specific skills, general cognitive abilities, and musicality abilities, indicating that there's a strong overlap between language aptitude and domain general skills in our data. The correlation between brain volume and thickness and the behavioural language aptitude scores resulted in no significant results after correction.

The behavioural results suggesting an overlap between general cognition and linguistics skills are consistent with previous work investigating a similar question in children, within a formal education context. Together these results suggest that language-specific skills have strong ties with general cognition, and that this overlap is stable across age and learning context. The lack of significant results in the structural MRI analysis might be due to a lack of power, arising from the statistically conservative analysis approach.

Next steps will involve using a multivariate analysis approach to explore the relationship between aptitude scores and thickness and volume of pre-selected regions of interest within the traditional language network.

Improving New Word Learning with High-Definition Transcranial Direct Current Stimulation

Farcy C.[2], Guggisberg A.[1],

Universitaire Neurorehabilitation University Hospital of Bern [1], University of Geneva [2]

Objective

Aphasia is a language disorder characterized by a disability in communication affecting writing, speaking or understanding. Current treatments do not allow a majority of patients to have access to a full recovery and, therefore, aphasia is often chronic. New treatments allowing patients to regain language functions are therefore necessary. Non-invasive brain stimulation techniques such as Transcranial Direct Current Stimulation (tDCS) are promising but effects remain inconsistent because it is still not known which areas and which neural processes need to be targeted to achieve better language recovery. Naming abilities are most frequently impacted in patients with aphasia and improving their capacity in this specific task is thus particularly relevant.

Our project aims to investigate the effects of high-definition (HD)-tDCS combined with new-word learning in healthy participants. We compare stimulation of two regions of interest: left inferior frontal gyrus (IFG) and left temporo-parietal junction (TPJ). We aim to investigate whether modulating functional connectivity (FC) of these regions facilitates learning new nouns or verbs. In view of previous studies, we expect to notice better performance in verb learning with left frontal gyrus stimulation and improved performance in nouns learning with left temporo-parietal junction.

Participants and Method

Thirty-six healthy subjects were recruited. They were randomly allocated to stimulation over either the left IFG, the left TPJ, or sham stimulation.

On day one, subjects performed a naming task (pre-test), which contained one hundred words represented as drawing. On day two, participants underwent a new-word learning task with rare words concurrently to HD-tDCS for 20 minutes. The final day consisted of a post-test of naming performance. Resting state EEG recordings were obtained on each day before and after the respective tasks.

Results

We observed a significant correlation between learning and a global decrease in alpha-band FC between Broca and the rest of the brain (WND). Conversely, theta-FC increased after stimulation between Broca's area and basal ganglia. We also observed an increase of theta-FC between Broca and Wernicke at day 3, which correlated with learning. At behavioral level, we observed better verb learning during Broca stimulation than sham stimulation. There was no significant effect on noun learning.

Conclusion

Resting state FC is an interesting neural target for therapy. Learning correlates with reduced global alpha FC (WND), and, instead, enhanced theta FC between key nodes of the language network. Enhancing FC seems to have an impact on learning capacities in healthy participants and also, as seen in previous studies with stroke patients, in clinical recovery. Also, verb recovery seems to be facilitated by Broca stimulation which is consistent with results of previous studies.

This suggests new neural targets for neuromodulation, which may enable more robust effects of brain stimulation in the future.

Memory

Why do individuals with Williams syndrome or Down syndrome fail the Weather Prediction Task?

Bochud-Fragnière E.[3], Lonchampt G.[3], Bittolo P.[3], Ehrensperger G.[3], Rita Circelli A.[1], Antonicelli N.[1], Costanzo F.[1], Menghini D.[1], Vicari S.[1], Lavenex P.[3], Banta Lavenex P.[2],

Bambino Gesù Children's Hospital, Rome, Italy[1], UniDistance Suisse[2], University of Lausanne[3]

Down syndrome (DS, Trisomy 21) and Williams syndrome (WS) are two neurodevelopmental disorders of genetic origin accompanied by mild to moderate intellectual disability. Although individuals with these syndromes exhibit different impairments in hippocampus-dependent place learning, they show enhanced striatum-dependent spatial response learning. Here, we used the Weather Prediction Task (WPT), which can be solved using different learning strategies dependent on distinct neurobiological systems, to determine whether individuals with DS or WS exhibit similar cognitive profiles outside the spatial domain. First, we evaluated whether individuals with WS (*n* = 38) and DS (*n* = 17) can solve the standard WPT. Second, we tested whether a concurrent hippocampus-dependent memory task may facilitate the reliance on a striatum-dependent learning strategy to solve the WPT in a subgroup of individuals with WS (*n* = 12). Third, we used four variants of a visual discrimination task to assess whether the deterministic or probabilistic nature of the cue-outcome association may influence the capacity of individuals with WS (*n* = 25) and DS (*n* = 14) to solve the WPT. Fourth, we assessed the influence of distractors on the capacity of individuals with WS (*n* = 27) and DS (*n* = 7) to solve the WPT. Only a small minority of individuals with WS and DS were able to solve the standard WPT. The use of a concurrent memory task failed to bias individuals with WS to use an efficient procedural strategy to solve the WPT. Both probabilistic feedback and distractors had a negative impact on the performance of individuals with DS and WS. Consistent with previous studies, this study suggests hippocampus-dependent learning impairments in WS and DS, and further reveals the importance of congruent feedback and low attentional demand to facilitate learning in individuals with DS and WS.

EEG correlates of fast categorization of L1 and L2 words in adults and children

Marca S.[4], Skieresz N.[5], Meziane H.[2], Gorin S.[2], Banta-Lavenex P.[2], Laganaro M.[3], Rothen N.[2], Reber T.[1],

UniDistance Suisse, University of Bonn Medical Center[1], Unidistance Suisse[2], University of Geneva[3], University of Geneva, UniDistance Suisse[4], University of Lausanne, Unidistance Suisse[5]

Semantic memory is essential to store knowledge about the world and to determine how to interact with one's environment (Binder et al., 2009; Binder &Desai, 2011; Martin &Chao, 2001; Volfart et al., 2021). It encompasses several abilities with differing levels of abstraction such as recognizing a tool, its use and its name, which elicit different neuronal activations, respectively (Binder et al., 2009; Binder &Desai, 2011). The latter ability, a linguistic ability, targets processes that go beyond simple perceptual processing (Binder et al., 2009). To better understand how semantic memory varies with level of abstraction, we tested whether the Fast Periodic Visual Stimulation (FPVS)-oddball paradigm is useful to assess Second Language Acquisition (SLA). Whereas recent findings from cognitive neuroscience showed the efficacy of this paradigm to measure the semantic categorization of images (Rossion et al., 2015; Stothart et al., 2017) and L1 (first language) words (Volfart et al., 2021), to our knowledge no study has used this paradigm to assess L2 (second language) semantic memory. Thus, the first goal of our study is to replicate Volfart's et al. (2021) findings with adults, and assess whether they extend to children. The second goal of our study is to assess whether the FPVS-oddball paradigm can assess semantic categorization in L2 in adults and children. Our results suggest that we can use the FPVS-oddball paradigm to assess successful L2 learning, as we identify a higher category-selective response after L2 learning compared to prior learning.

Investigating the role of hippocampus in sleep-dependent perceptual memory consolidation

Banterle L.[1], Foustoukos G.[1], Osorio-Forero A.[1], Cherrad N.[1], Fernandez L.[1], Lüthi A.[1],

University of Lausanne[1]

The sleeping brain is thought to support offline memory consolidation in two distinct phases. First, the hippocampus rapidly encodes aspects of the awake learning experience. Then, the newly acquired hippocampal information is thought to be replayed repeatedly during non-rapid eye-movement sleep (NREMS) driving synaptic plasticity in cortical circuits, allowing long-term memory storage. Amongst the many learning tasks executed by rodents, goal-oriented sensorimotor tasks have been well characterized in terms of the site and timing of cortical circuit plasticity. This offers us the chance of studying the role of sleep's electrical brain rhythms in the setting of a defined cortical circuit engaged in the learning of a controlled paradigm. We chose a two-tone auditory discrimination task that required head-fixed and water-restricted mice to discriminate between a Go- (8 kHz) and a No-Go (12 kHz) tone to obtain a water reward. Mice learned over 7-14 days to become experts (d' = 1.5 –2). Once the mice reached the expert criterion, the sounds contingencies were reversed. Across days, mice improved performance by reducing the False Alarm rate, which corresponds to the No-Go tone response, and by suppressing unspecific licking ahead of the tones. We monitored sleep longitudinally across all experimental sessions, to take into account adaptive sleep changes caused by water restrictions and habituation to head-restraint. We are now focused on the role of the hippocampus, involved both in the awake processing and in the offline consolidation, in sleep-dependent learning of the task. For this purpose, we selectively silenced the hippocampal activity by means of a closed-loop system and optogenetics during 6 h of post-learning NREMS. Preliminary data suggest that hippocampal activity during post-learning NREMS appeared to be essential for the reversal learning paradigm because suppression of its electrical activity prevented reversal learning. Together, our work is a first step towards defining the hippocampal involvement in sleep-dependent consolidation of perceptual memories, and to determine how it interacts with adaptive sleep changes that are a natural part of daily learning experience.

Brain-wide Epigenetic Mapping of Fear Memory Engram Cells

Yip K.[1], Gräff J.[1],

EPFL[1]

A memory engram is thought to be the physical substrate of the memory trace within the brain, which is generally depicted as a neuronal ensemble activated by learning to fire together during encoding and retrieval. Nowadays, emerging evidence supports the postulation that memory engram exhibits a multiscale organization both at a brain network level and at an epigenetic state. However, as engram cells have mainly been visualized in a limited number of brain regions, functionally connected engram ensemble complex distributed across the entire brain have only started to be illustrated. Furthermore, as epigenetic mechanisms underlying memory formation and storage have mainly been studied at heterogeneous whole tissue level, engram cell-specific epigenetic modifications have only started to be elucidated. To fill these loopholes, our project aims to generate a composite image of whole brain fear memory engram epigenetics (aka epi-engram) throughout memory consolidation. By applying iDISCO+ optical clearing, light sheet microscopy and semi-automated 3D colocalization analysis, we overcome the technical bottleneck of whole mount multiple immunostaining to visualize activity-tagged neurons in the TRAP2-tdTomato mouse line, concomitantly with the neuronal activation marker *cfos* and histone modifications. We hope that brain-wide epi-engram mapping will ultimately illustrate a model how engram cell states are orchestrated by chromatin states.

Signal Detection and Decisional Components Influence Electrophysiological Correlates of Recognition Memory

Schneider S.[2], Coll S.[2], Schnider A.[1], Ptak R.[1],

University Hospitals Geneva[1], University of Geneva[2]

Human recognition memory appears to have almost infinite capacity. Debates around its underpinnings have benefited from evidence provided by evoked potential (ERP) studies leading to a relative consensus around a dual-process account given different ERPs patterns related to familiarity vs. recollection. However, such studies solely investigate correct answers and might not represent the full scope of recognition memory. Signal detection theory (SDT) does so by using four response types (hit, miss, correct rejection, false positive). Here we argue that using SDT and a model-free approach on ERP data will further our understanding of recognition memory.

Twenty-three participants encoded 360 images of various categories presented for 750 ms and were asked to identify the 360 “old” images intermixed with 360 “new” images 24 hours later, while a 128-channels EEG was recorded.

To identify spatial and temporal ROIs, we conducted a waveform non-parametric repeated-measure ANOVA on the type of SDT response type across all electrodes, timeframes, and ERPs. Three spatial ROIs were identified as predictors of performance: two posterior (left and right) and one medio-central cluster. One temporal ROI (470 to 670ms) returned significant differences. Post-hoc tests revealed an effect of acceptance vs. rejection (i.e., yes vs. no) on the frontal cluster while hit, miss, correct rejection, and false positive responses were differentiated posteriorly.

This study suggests that incorporating all response types in a complex recognition memory task yields results that are only partly consistent with the existing literature. It prompts the need to further investigate all response types in recognition memory.

The N400 as neurophysiological marker of second-language learning

Skieresz N.[5], Marca S.[4], Gorin S.[2], Murray M.[1], Reber T.[3], Rothen N.[2],

Lausanne University Hospital and University of Lausanne, CIBM, Vanderbilt University[1], UniDistance Suisse[2], UniDistance Suisse/Department of Epileptology, University of Bonn Medical Center, Bonn 53127, Germany[3], University of Geneva/UniDistance Suisse[4], University of Lausanne/UniDsitance Suisse[5]

Research on memory has identified various learning strategies that support knowledge acquisition. Some of the most effective strategies are retrieval practice (i.e., actively recalling information), multimodal learning (i.e., presenting information via multiple sensory modalities), and corrective feedback (i.e., receiving the correct response when making an error). While each strategy has been examined separately, interactions between them and their underlying neurophysiological correlates remain to be investigated. Our study aims to investigate potential interactions between the learning strategies on associative memory (vocabulary acquisition) and their neurophysiological correlates, focusing on the N400 event-related potential –a marker for semantic violations. Adults learned Finnish (L2) vocabulary using a mobile application where the proportion of retrieval, multimodality, and feedback on individual translations were varied. Before and after 14 days of learning, vocabulary knowledge was assessed in a vocabulary test and a recognition task, where correct and incorrect translations had to be identified while EEG was recorded. We assessed the correctness of responses and compared the N400 for correct and incorrect translations by learning strategy. We hypothesized that incorrect vs. correct translations elicit an N400 after learning to index vocabulary acquisition. We expected this effect to be modulated by combinations of different learning strategies. Preliminary results show that vocabulary learning was successful and indicate a modulation in the N400 window. Learning strategies did not modulate the participants performance. These results suggest that the N400 can be used as marker for L2 vocabulary learning.

Inhibition of claustro-splenial projections improve the retrieval of a remote fear memory

Renfer J.-R.[2], Mutel S.[1], Rodriguez I.[1], Carleton A.[1], Salazar R.[3],

University of Geneva[1], University of Geneva, Centre medical universitaire[2], University of geneva [3]

Contextual memory of past traumatic events relies on a dynamic and long-lasting neuronal trace. This trace is widespread throughout the cortex and spans across multiple areas. We hypothesized that the claustrum, a subcortical structure connecting the whole cortex, is a critical node within the “memory retrieval” neuronal network for a remote (one month) but not for a recent (a few days) memory. First, we tested this hypothesis by inhibiting Slc17a6 claustral neurons using the Vglut2-cre mouse line and chemogenetic tools; Vglut2 being a specific local marker of the claustrum. As this putative inhibition did not affect the retrieval of a fear memory for either a recent or a remote memory, we further investigated whether specific claustral projections (rather than specific genetic identity) may play such a role. In wild-type mice, claustral projections to the medial prefrontal cortex and to the retrosplenial cortex, two areas involved in the retrieval of a remote fear memory, were targeted using a retrograde cre-dependent method . The putative chemogenetic inhibition of claustro-prefrontal projections did not affect fear memory retrieval for both a recent and a remote memory. However, to our surprise, the putative inhibition of claustro-splenial projections increased the freezing response during the retrieval of a remote contextual fear memory. This effect was not observed during either the retrieval of a recent contextual memory or during the presentation of the conditioned stimulus. These results suggest that different populations of claustral neurons characterized either by their genetic identity or by their projection profiles have different functional roles in contextual fear memory.

Learning from fictional sources in a virtual reality environment

Dall'Olio L.[1],

University of Lausanne[1]

Learning from fictional sources in a virtual reality environment

LNDS annual retreat 2022

Dall'Olio Lucas, Martarelli Corinna

New technologies are taking an increasingly important place in our society. Their arrival in the world of education through the digitalization of educational tools and materials is inevitable. However, there is a lack of empirical evidence on how they affect children's learning and memory abilities.

The aim of this study was to investigate the educational impact of a presentation in a virtual setting. To do so, our participants had to follow a presentation, either in immersive virtual reality (IVR) using a virtual reality headset or in non-immersive virtual reality (N-IVR) simply following the presentation on a tablet. We also investigated how the realism of the presentation would impact the participants' memory abilities. The presentation would either be given by a little girl (realistic condition) or an anthropomorphic animal (unrealistic condition). Afterwards, the participants had to carry out 3 different memory tasks –a new/old recognition task, a quiz, and a transfer task. To investigate long-term retention, participants were asked to complete these tasks twice –on the same day and one week later. Finally, we controlled the theory of mind and verbal comprehension skills of the children. In total we interviewed 168 4-6-year-old children –47 in the VR realistic condition, 45 in the VR unrealistic condition, 36 in the tablet realistic condition and 40 in the tablet unrealistic condition.

Contrary to our expectations, the children performed significantly worse in the VR condition when compared to the tablet condition. One possible explanation would be that VR requires more cognitive resources from the participating children. As expected, children performed better in the realistic condition, especially one week after the presentation. This confirms the hypothesis that children tend to retain less information if they are deemed unrealistic particularly in the long run.

Neurological and (neuro)psychiatric conditions

Navigation on virtual reality tasks is abnormal in patients with bilateral vestibular loss

Boutabla A.[3], Ahmad M.[2], King S.[4], S. Panic A.[1], Karmali F.[4], Chari* D.[4], Lewis* R.[4],

Ashton Graybiel Spatial Orientation Lab, Brandeis University, Waltham, MA [1], Department of Otolaryngology – Head and Neck Surgery, UMASS Memorial Medical Center, University of Massachusetts Medical School, Worcester, MA [2], Division of Otorhinolaryngology Head and Neck Surgery, Geneva University Hospitals and University of Geneva, Geneva, Switzerland [3], Jenks Vestibular Physiology Laboratory, Massachusetts Eye and Ear, Boston, MA [4]

Accurate spatial navigation requires humans to estimate their position within an environment and track their changes in position and orientation, using both idiothetic (body-centered) cues from vestibular, proprioceptive, and efferent sources and allothetic cues (e.g. visual landmarks). Vestibular information, which encodes the angular and linear motion of the head in space, is crucial for precise navigation. Yet, the literature on navigational abilities in patients with peripheral vestibular damage is inconsistent. In our study, we compared navigation abilities in patients with bilateral vestibular loss (BVL) and normal control (NC) subjects in a virtual reality (VR) spatial navigation "triangle completion task" in two conditions: 1) *dynamic*, in which subjects had access to visual, vestibular, proprioceptive, and efferent sensory signals and 2) *stationary*, in which subjects relied only on visual cues. We found that male BVL subjects had decreased accuracy and precision on the dynamic navigation task compared to NC. In addition, while BVL males were less precise in the dynamic task compared to the stationary task, NC males were comparatively more precise in the dynamic task. BVL male subjects further demonstrated longer mean path lengths in the dynamic task compared to male NC subjects. Interestingly, Female BVL and NC subjects performed similarly on both dynamic and stationary tasks. Overall, our findings suggest that aberrant vestibular motion cues may degrade the estimate of position within the VR environment. Further research is needed to characterize the specific contributions of idiothetic cues on dynamic navigation tasks and to better understand sexual differences in vestibular function.

Principles of gait encoding in the subthalamic nucleus of people with Parkinson's disease

Thenaisie Y.[3], Lee K.[4], Moerman C.[3], Scafa S.[3], Courtine G.[2], Bloch J.[1], Martin Moraud E.[1],

Neurorestore / CHUV[1], Neurorestore / EPFL[2], University of Lausanne / CHUV[3], Wyss Center[4]

Disruption of subthalamic nucleus (STN) dynamics in Parkinson's disease leads to impairments during walking. Commonly used therapies such as STN deep brain stimulation (DBS) has limited efficacy on severe gait deficits. Here, we aimed to uncover the principles through which the STN encodes functional and dysfunctional walking in people with Parkinson's disease.
We first conceived a neurorobotic platform that allowed us to deconstruct the key components of walking under well-controlled conditions. We exploited this platform in 18 patients with Parkinson's disease, which allowed us to demonstrate that the subthalamic nucleus encodes the initiation, termination, and vigor of leg muscle activation during single-joint leg motor tasks. We identified low (~13-20Hz) and high beta (~20-35Hz) desynchronization time-locked to effort initiation, adaptation and termination, followed by a beta rebound. These modulations were present during passive and active movements. Surprisingly, these modulations were present in STN ipsi- and contralaterally to the active leg. Maintaining stronger efforts implied stronger desynchronizations.

We then mapped STN activity patterns to whole-body kinematics, and leg muscle activity during a variety of locomotor tasks (standing, walking with different step length, turning). We found that the same fundamental principles determine the encoding of walking. Despite patient-specific idiosyncrasies, we identified similar patient-specific band modulations during gait tasks. Gait initiation, adaptation and termination were marked by beta desynchronizations and were efficiently decoded. STN activity also exhibited a phasic step length-dependent pattern during the gait cycle, which allowed decoding left versus right gait phases.
We finally translated this understanding into a machine-learning framework that decoded muscle activation, walking states, locomotor vigor, and freezing of gait. These results may guide the decoding of abnormal gait patterns in PD, such as asymmetry, shuffling steps or freezing of gait. Such biomarkers guide the design of adaptive stimulation protocols specifically addressing gait deficits.

WHITE MATTERS: A MULTIMODAL MRI INVESTIGATION OF STRUCTURAL CONNECTIVITY AND WHITE MATTER INTEGRITY IN ANOREXIA NERVOSA: FROM HIGH-RISK OFFSPRING TO PATIENTS

Borsarini B.[1], Micali N.[1],

University of Geneva[1]

Anorexia nervosa (AN) is a severe psychiatric disorder with an early onset age and with one of the highest long-term mortality. Evidence is growing on the impact of AN in executive functions and at the brain level.
White matter (WM) microstructure alterations have been shown in patients with AN. However, findings from diffusion tensor imaging (DTI) studies of WM integrity and connectivity in AN are still scattered. Additionally, although offspring of AN patients are known to be at high-risk for the disorder, no neural investigations on possible AN biomarkers have been carried out so far.
Therefore, the present doctoral proposal intends to reduce this gap in the literature by means of four projects: 1) A DTI investigation of structural connectivity in AN high-risk offspring; 2) A correlational study including structural connectivity, body image perception and executive functions (Spatial Working Memory, Cognitive Flexibility and Inhibitory Control) in AN high-risk offspring; 3) An Ultra-High Field (UHF) 7T DTI investigation of structural connectivity and WM integrity in patients with AN; 4) An UHF 7T investigation of intracortical myelin organization in AN.
Preliminary results from the first project are promising. Differences in Fractional Anisotropy (FA) as a measure of structural connectivity have been found between seven at-risk and seven control girls in regions already-known to be involved in AN.
This integrative approach can be strategic for answering outstanding issues regarding neurobiology and biomarkers of AN. Least but not last, it could provide findings for predicting patients' therapeutic response and improve treatment for AN.

STIMO-PARKINSON: Study on feasibility of Targeted epidural spinal stimulation to Improve MObility in patients with PARKINSON's disease.

Moerman C.[2], Martin Moraud E.[1],

CHUV[1], CHUV-UNIL[2]

More than 90% of individuals with Parkinson's disease (PD) suffer from considerable locomotor disturbances that affect their quality of life[1]. These deficits respond poorly to current available therapies such as dopaminergic medication and deep brain stimulation[2-4]. Gait and balance deficits are in part due to the disruption of the communication between the brain and spinal cord resulting from the depletion of dopaminergic and cholinergic circuits[5].
Rather than stimulating the classical dopaminergic pathways in the brain to address these deficits, we targeted the proprioceptive feedback circuits located within the dorsal roots projecting to the spinal cord regions controlling leg movement. Following encouraging results in the 1–methyl–4–phenyl–1,2,3,6–tetrahydropyridine (MPTP) nonhuman primate (NHP) model of PD, we transferred this potential therapy to a clinical trial by using a Medtronic spinal implant with real-time stimulation modulation capabilities. We designed electrical spinal cord stimulation protocols and linked them to specific gait phases with the help of inertial measurement units (IMU) to reproducing natural spatiotemporal muscle activations during walking. This targeted spinal cord stimulation instantly reduced freezing of gait and improved the walking speed and gait quality in our first participant with PD.

Author list:
Charlotte Moerman, Nicolo Macellari, Camille Varescon, Lea Bole Feysot, Gaia Carparelli, Cathal Harte, Alice Bruel, Sergio Daniel Hernandez-Charpak, Gregory Dumont, Nicolas Hankov, Molywan Vat, Anne Watrin, Aurélie Paley, Manon Tschopp, Natacha Hermann, Valentin Lupi, Fabio Becce, Etienne Pralong, Mayte Castro Jiménez, Julien F. Bally, Léonie Asboth, Robin Demesmaeker, Tomislav Milekovic, Jocelyne Bloch, Gregoire Courtine* and Eduardo Martin Moraud**

The NAD+ precursor NMN activates dSarm to trigger axon degeneration in Drosophila

Llobet Rosell A.[1], Neukomm L.[1],

University of Lausanne[1]

Axon loss is the earliest detectable feature of challenged and diseased nervous systems. Yet underlying molecular mechanisms executing axon degeneration remain poorly understood.
Injury-induced axon degeneration is a well-established and simple system to study how axon death signaling executes axon degeneration. In *Drosophila*, the labile enzyme dNmnat is synthesized in the soma, transported into the axon, and rapidly degraded. Low abundant dNmnat is sufficient to convert the precursor nicotinamide mononucleotide (NMN) into nicotinamide adenine dinucleotide (NAD^+). Upon axonal injury, the axonal supply of dNmnat ceases, and remaining dNmnat is promptly degraded, which results in a rise of NMN and a halt in *de novo* NAD^+ synthesis. The increase of the NMN/ NAD^+ ratio activates the NADase dSarm, which pathologically depletes NAD^+ culminating in the degeneration of severed axons.
Here, we demonstrate that lowering the levels of the precursor NMN in *Drosophila*–through the expression of the prokaryotic enzyme NMN-Deamidase (NMN-D)–preserves severed axons for months and keeps them circuit-integrated for weeks. NMN-D alters the NAD^+ metabolic flux by lowering NMN, while NAD^+ remains unchanged *in vivo*. In contrast, severed axons with elevated NMN levels degenerate faster than wild-type axons. Finally, we show that NMN induces the activation of dSarm to execute axon degeneration *in vitro* and *in vivo*. Our work reveals a pro-degenerative function of NMN in injury-induced axon degeneration in *Drosophila.*
Axon death signaling is activated in diseased and challenged nervous systems without injury. Understanding axon death signaling mechanisms could help define therapeutic targets to block axon loss.

Monitoring Accuracy Of Home-Based Non-Invasive Brain Stimulation Using A Novel Electrode Localization Algorithm

Windel F.[1], Gardier R.[1], Fourchard G.[1], Viñals Terres R.[1], Thiran J.-P.[1], Morishita T.[1], Hummel F.[1],

EPFL[1]

In addition to medication, physio- and psychotherapy, non-invasive brain stimulation (NIBS) has been suggested to be of additional value to treatment strategies for psychiatric and neurologic diseases (Brunoni et al., 2012, Hummel &Cohen, 2006, Palm et al., 2014). Home-based, self-applied solutions have, in this context, been promoted to ensure a larger outreach and regular high-frequency treatment exposure (Palm et al., 2018). However, there are currently no available solutions for researchers and clinicians to monitor the correct placement of stimulation electrodes in the home-based setting. To address this issue, we have developed an easy-to-use and cost-efficient tool to support patients at home. Using a standard tablet and its in-built camera, this novel algorithm detects individual facial key points and QR-like markers to identify the placement of the cap holding the electrodes in 3D space. It then provides patients with real-time feedback to adjust the cap's position. To test feasibility and accuracy of this solution, we recruited 36 healthy participants and compared their cap placement performance with a reference cap placement by a trained investigator. We compared participants placement accuracy with instructions before (*Pre*) and after the investigator's placement (*Post*) as well as participants using the support tool (*AlgorithmB*). Electrode positions were captured using a Neuronavigation system. A Friedman Rank Sum test did not show a significant difference in accuracy between the three conditions. Permutation tests demonstrated a significantly smaller deviation in the *AlgorithmB* compared with the *Pre* cap placement, however *Post* and *AlgorithmB* conditions did not differ. Subjective measures, in form of visual analogue scales measuring confidence, easiness to use and usefulness of the solution averaged around 8 out of 10. Importantly, the algorithm decreases the variability of performance in cap placement accuracy visibly and ensured placement within the suggested maximum of deviation (10 mm; Woods et al., 2015, Opitz et al., 2018) in 34 out of 36 participants. This novel technology furthermore provides, for the first time, a way to monitor the electrode placement at home, creating a form of evaluation in a session-by-session manner. We believe that this set-up improves the status quo of home-based NIBS in developing a comfortable and controlled environment for patients in the future. It may therefore add to the body of research that is working towards high frequency treatment strategies that are accessible and can be integrated in patients' everyday life.

Frontal and limbic functional connectivity patterns are associated with APOE4 and remain consistent over different stages of Alzheimer disease.

Fall A.[1],

University of Geneva[1]

AD is the most common cause of dementia in older adults. There's consensus among experts that an effective treatment needs to be administered as early as possible to either slow down the progression of the disease and maybe even reverse it. Advanced fMRI technics may be used to characterise brain change at earliest disease stages of AD. To this effect my project aimed at providing knowledge of AD detection.Various risk factors for this disease, such as biological and genetical, have been investigated in the last decades. Apolipoprotein E4 (APOE4) is the strongest known genetic risk factor for AD. There is three major versions of the gene (allele) in humans E2 vs E3 vs E4. Having 2 ApoE4 allele represents a genetic risk factor 10 time higher than having 2 ApoE2 allele for late-onset sporadic AD.

Therefore, the aim of our study is to provide a better understanding of brain functionnal connectivity in individuals having the genetic risk factor. Our principal hypothesis is that individuals with at least one ApoE4 allele present a different brain functional connectivity compared to non-carriers.

To answer this question, we took our data from the Alzheimer's Disease Neuroimaging Initiative database ; 140 study participants in total (42: Cognitive Normal, 38: Subjective Memory Complaint, 46: Mild Cognitive Impairment, 14: Alzheimer's Disease). We computed the static functional connectivity (FC) of each subjects. We investigated 2 different approach of functional connectivity regional properties, the eigenvector centrality that tell us how central a region is and the node strength that give us a sense of how much a region is connected in the network. In those both analysis we compared the individuals having at least one ApoE4 allele and those who don't.

The non-parametric Kruskalwallis test on our 2 groups E4 carriers versus non-carriers showed 50 regions that present different centrality with the rest of the brain in ApoE4 carriers compared to non carriers. In fact, we found that the ApoE4 individuals presented different eigenvector centrality in the paracentral lobular and mid cingulate cortex. This difference was seen in dorsal area as well as the ventral part of the paracentral lobular and mid cingulate cortex (X^2=6.565, p-val=0.01), region known to be altered in the Alzheimer's disease patients. 41 regions that present lower connectivity strength in ApoE4 carriers compared to ApoE4 non carriers. In fact, we established that in the anterior cingulate and medial prefrontal cortex seems to present lower connectivity strength in the ApoE4 carriers compared to non-carriers (X^2= 4.875, p-val= 0.027). Those regions are known to be part of the default mode network, that present a disruption in AD individuals (Seeley et al., 2009).

Our findings suggest that consistent patterns of resting state FC are associated with carrier status of the ApoE4 allele. This pattern was present at various stages of AD progression and AD risk status: CN,SMC,MCI,AD. The identified connectivity patterns might serve as response markers for disease modifying therapeutical intervention at early disease stages.

The impact of intestinal microbiota on the encephalitogenic properties of CNS-specific Th17 cells

Rebeaud J.[1],

University of Lausanne[1]

Background: Multiple sclerosis (MS) and its animal model, experimental autoimmune encephalomyelitis (EAE) are demyelinating diseases of the central nervous system (CNS). MS and EAE are mediated by auto-reactive CNS-specific T cells that are activated in the periphery and penetrate through the blood-brain barrier (BBB) into the brain parenchyma. The gut microbiota is identified as an emerging environmental factor involved in MS and its implication in MS pathogenesis needs to be further characterized.
Hypothesis: CNS-specific Th17 cells acquire encephalitogenic properties by interacting with the gut microbiota during colonic lamina propria infiltration.
Methods: We used the Th17 cell adoptive transfer model of EAE. Mice were treated with large spectrum antibiotics before and during EAE to assess the role of the gut microbiota in EAE adoptive transfer. Isolation and characterization of immune cells from the colonic lamina propria and the brain by flow cytometry were performed during EAE. Furthermore, Th17 cells were treated with fecal metabolites extracted from stools of mice treated or not with antibiotics.
Results: Antibiotic treatment attenuates Th17-cell adoptive transfer EAE disease and reduces the absolute number of CNS-specific Th17 cells infiltration in the CNS. Antibiotic treatment also modifies CNS-specific Th17 cells' transcriptomic and phenotypic profiles in the gut. Indeed, it reduces the pathogenic signature of Th17 cells and their expression of the pro-inflammatory cytokine IFNg and of the chemokine receptor CXCR6. *In vitro* treatment of CNS-specific Th17 cells with fecal metabolites extracted from stools of control mice enhance their pathogenicity in a microbiota-dependant manner. Indeed, Th17 cells treated with fecal metabolites coming from stools of control mice induce IFNg secretion as well as CXCR6 expression whereas fecal metabolites from stools coming from antibiotic-treated mice do not. Finally, we adoptively transferred Th17 cells previously treated with fecal metabolites extracted from stools of control mice and observed an increased EAE disease severity.
Conclusion: Those results suggest that bacteria from the gut microbiota produce microbial metabolites which enter in contact with injected myelin-specific 2D2 Th17 cells in the colonic lamina propria and induce a pathogenic switch from stem-cell-like Th17 cells to pathogenic Th17 cells expressing CXCR6 and secreting IFNg. The pathogenic cells then migrate to the CNS and induce EAE disease. Upon antibiotic treatment, gut bacteria and gut microbial metabolites are diminished which reduces CXCR6 expression and IFNg secretion which impacts their migratory abilities and dampens EAE disease severity.

Single-cell topography enables regeneration across a complete spinal cord injury and restores walking

Milano M.[1], Squair J.[1], Courtine G.[1], Anderson M.[1],

EPFL[1]

Although axon regeneration can now be induced experimentally across anatomically complete spinal cord injury (SCI), restoring meaningful function after such injuries has been elusive. This failure contrasts with the spontaneous, naturally occurring repair that restores walking after severe but incomplete SCI. Here, we performed projection specific and comparative single-nucleus RNA sequencing to identify the transcriptional phenotype and connectome of neuronal subpopulations involved in natural spinal cord repair. We identified a molecularly defined population of excitatory projection neurons in the thoracic spinal cord that extend axons to the lumbar spinal cord where walking execution centers reside. We show that regrowing axons from these neurons across anatomically complete SCI and guiding them to their appropriate region in the lumbar spinal cord restores walking in mice. These results demonstrate that mechanism-based repair strategies that recapitulate the natural topology of molecularly defined neuronal subpopulations can restore neurological functions following anatomically complete SCI.

Establishing the evolutionary conserved and divergent transcriptional programs after spinal cord injury across non-human primates, rodents and zebrafish

Regazzi N.[1],

University of Lausanne[1]

Nicola Regazzi, Jordan W. Squair, Thomas H. Hutson, Michael A. Skinnider, Matthieu Gautier, Teo Yue Yang, Simon Borgognon, Katia Galan, Charles Latchoumane, Quentin Barraud, Mark Anderson, Claudia Kathe, Jocelyne Bloch, Grégoire Courtine

In adult mammals, the initial trauma induced by a spinal cord injury (SCI) is rarely itself the primary determinant of neurological outcome. Instead, it is the trigger for a complex and progressive cascade of secondary processes that ultimately lead to a non-regenerative environment around the lesion site, leaving very little opportunity for functional recovery. In primates, this phenomenon is even more true and neuronal networks of the spinal cord show very few signs of repair. Conversely, invertebrates and phylogenetically primitive vertebrates such as zebrafish or salamanders possess a higher regenerative capacity allowing them to spontaneously regrow axons through the lesion core and regain extensive sensorimotor functions. However, how the individual types and subtypes of cells of the central nervous system (CNS) coordinate to mediate such different responses to SCI remains poorly understood.

Here, using both immunohistochemical approaches and single-nucleus RNA-sequencing (snRNA-seq) of the spinal cords lesion site, we are comparing the evolutionary conserved and divergent transcriptional programs after SCI in highly regenerative species such as zebrafish and Acomys, and in less regenerative species such as mice, rats and non-human primates, that lead to these different anatomical and functional outcomes. To achieve this goal, we first established spinal cord injury models in zebrafish, Acomys, mice, rats and non-human primates that ensure the activation of similar transcriptional programs and identified 3 key-timepoints to capture the uninjured, acute and chronic state after SCI. Using high-precision kinematics recordings at regular timepoints of the whole body, we investigated the spontaneous behavioural recovery potential in each species. We validated our SCI models histologically using classic immunohistochemistry and 3D imaging of the lesion site after clearing. Additionally, we harvested fresh tissue for snRNA-seq of the lesion sites. Finally, we will exploit bioinformatic tools to perform comparative analysis and highlight the biological differences between all the species' responses to SCI that may have precluded thus far the translation of promising preclinical therapies to clinics. Including regenerative models such as zebrafish and Acomys will simultaneously open new avenues for targeting molecular mechanisms involved in regeneration.

Regulating GDNF gene therapy: toward a successful treatment for Parkinson's disease?

Duarte Azevedo M.[1],

CHUV[1]

Glial cell line-derived neurotrophic factor (GDNF) protects nigro-striatal dopaminergic (DA) neurons and reduces motor symptoms when applied in the striatum in toxin-induced Parkinson's disease (PD) models. Furthermore, GDNF protects midbrain DA neurons against alpha-synuclein propagation in mice model induced by pre-formed fibrils[1].
However clinical trials based on intraputaminal GDNF delivery has so far failed to demonstrate significant clinical benefits[2].
GDNF is also known to interfere with dopamine homeostasis via time and dose-dependent neurochemical effects[3]. Our hypothesis is that depending on the delivery parameters, these neurochemical effects could be deleterious and mask or reduce GDNF beneficial effect.
Methods
We have described a doxycycline (dox)-regulated viral vector (AAV-DoxON-GDNF) which allows to finely adjust GDNF dose and period of administration at clinically-acceptable antibiotics doses[4].
We have then injected a high dose of the AAV-DoxON-GDNF vector in order to mimic conditions of GDNF overdosing in a unilateral 6-OHDA rat model. Using Dox regulation, we have administered GDNF at 2 different concentrations: 4-fold (GDNF-LOW) and 20-fold (GDNF-HIGH) higher than the endogenous striatal level. The treatment period was 17 weeks either continuously or transiently for 2 weeks with 2 weeks interruptions.
Results
At 16 weeks post-injection, the GDNF-LOW group and GDNF-HIGH-intermittent groups showed a significant reduction of the behavioral asymmetry while the GDNF-HIGH-continuous group did not show significant improvements.
Conclusions
In future clinical trials, it will be important to regulate GDNF administration in order to avoid overdosage potentially reducing the clinical benefits.

Hippocampus and Claustrum networks alterations in mice model of schizophrenia

Moulinier M.[1],

University of Geneva [1]

To study schizophrenia (SZ), several mouse models were developed. The LgDel line, model of the highest identified genetic factor to develop SZ in humans, was previously used in the lab. We have demonstrated a reduction of LgDel$^{+/-}$ pyramidal cells coactivation in the CA1 region of the hippocampus (HPC). Here, we used another model of SZ: the Nr4a2 heterozygous knock-out. We showed that their CA1 circuits are displaying the same reduced co-activation as the LgDel mice. In parallel, an *in vivo* study from the lab highlighted a reduction of specific cell assemblies in the claustrum (CLA) of Nr4a2$^{+/-}$ mice compared to wild-type. Thus, we wondered if the CLA would display the same co-activation alterations as the HPC. To this extent, we were able to developed organotypic slices of the CLA and record its neuronal network activity using calcium imaging. We highlighted that CLA circuits were able to fire similarly to the CA1 ones. Moreover, we showed that Nr4a2$^{+/-}$ CLA neurons are displaying a reduction of co-activation. In conclusion, circuits alterations are kept among models of SZ and brain regions relevant to SZ, implying that reduced co-activation might be a phenotypic marker of the disease. Finally, to dissect CLA circuits we performed patch-clamp experiments. We showed that Nr4a2$^{+/-}$ CLA neurons have a lower firing frequency than WT. In addition, this difference is kept when pharmacologically blocking glutamatergic and GABAergic transmission; implying that the frequency alterations may not be due to a difference in synaptic inputs, but rather to changes in the cells intrinsic properties.

Preservation of cardio-audio regularity processing as a predictor of coma outcome

Pelentritou A.[1],

University of Lausanne[1]

Healthy volunteers can infer on the temporal relationship between cardiac and auditory stimuli in predicting future auditory events. Whether this inference can occur in the absence of consciousness remains unknown. Here, we address this question by investigating implicit auditory prediction in comatose patients during the first day of coma, i.e. a deep unconscious state. We recorded continuous electrocardiography (ECG) and electroencephalography (EEG) in 57 comatose patients (35 survived beyond unresponsive wakefulness at three months). We acquired a baseline condition or presented auditory sequences at a fixed pace (isochronous) or in synchrony or asynchrony to the ongoing heartbeat, interrupted by rare sound omissions. Cluster permutation statistical analysis ($p<0.05$, two-tailed) assessed the EEG omission responses across auditory regularity conditions. In coma survivors, the neural response to sound omissions differed in the comparison synchronous against asynchronous and synchronous against baseline (at 253ms to 338ms and at 251ms to 430ms following heartbeat onset, respectively). All statistical tests performed in coma non-survivors provided no significant results. The unconscious brain can generate an expectation of upcoming sounds depending on the temporal contingency between heartbeat and sound as previously observed in healthy awake participants. This evidence informs on the degree of two preserved neural processes important for survival in patients with good prognosis: the neural processing of bodily signals and their integration in relation to environmental sensory stimuli. How the human brain monitors temporal regularities across cardiac and auditory inputs in deep unconscious states presents a potential biomarker for coma outcome prediction.

Development of a CRISPR-Cas9 system for ATXN3 gene editing in Spinocerebellar ataxia type 3 disease

Rybarikova M.[1],

CHUV[1]

Spinocerebellar ataxia type 3 (SCA3) is a rare neurodegenerative disease caused by an unstable repeat expansion encoding cytosine-adenine-guanine (CAG) within the exon 10 of ATXN3 gene. This polyQ expansion results in a toxic gain of function of ataxin-3 protein resulting in neuronal dysfunction and death particularly in the cerebellum. Patients with the mutant ATXN3 suffer from poor motor coordination and cognitive dysfunction. Currently, there are no available permanent treatments for the SCA3 but with the recent developments in gene therapy, new curative options are being increasingly researched. In this project, we implement CRISPR/Cas9 system for ATXN3 gene editing as a potential SCA3 therapy in following strategies: 1. ATXN3 inactivation through exon 1 targeting. The strategy implicates single guide RNA (sgRNA) targeting the endogenous human ATXN3 gene at its translational start site in exon **1.** This leads to ATXN3 inactivation by blocking ataxin-3 protein production. We complement this strategy with gene replacement therapy, since we will also deliver a wild-type ATXN3 gene. **2.** Non allele-specific exon 10 deletion. A pair of sgRNAs flanking the exon 10 (containing the CAG repeats) of ATXN3 will result in deletion of the entire exon comprising both the wild-type (WT) and mutant ATXN3 (muATXN3). This will generate truncated, but functional protein. **3.** Exon 9 targeting of the ATXN3. The goal is to generate small insertions or deletions (indels) and introduce a shift in the open reading frame (ORF)/introduce an early stop codon, resulting in a truncated but still functional protein.

Other

ROLE OF EPHRINBS IN REGULATION OF POMC NEURONS EXCITABILITY IN A DIET-INDUCED PREDIABETES IN MICE.

Pajot C.[1], Labouèbe G.[1], Emmenegger Y.[1], Vaucher A.[1], Thorens B.[1], Croizier S.[1],

University of Lausanne[1]

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, notably hepatic glucose production and insulin secretion. Literature suggests that these functions can be mediated through the ability of POMC neurons to sense peripheral information, notably glucose level. In addition, POMC neurons receive direct upstream excitatory (glutamate) and inhibitory (GABA) inputs from a plethora of brain areas. A study from our group specifically showed that manipulating well-known actors of glutamatergic synapse formation called EphrinBs, reduced the number of glutamatergic inputs into POMC neurons, impaired their excitability and insulin secretion in response to hyperglycemia. Interestingly, these molecules are still expressed in POMC neurons in adult mice. While we described a role of these EphrinBs in the development of excitatory inputs into POMC neurons, we still do not know the role played by these molecules notably in term of synaptic plasticity, and glucose homeostasis.

Here, we fed male and female mice either a control diet or a high fat high sucrose diet progressively leading to weight gain, insulin resistance and glucose intolerance. By using this mouse model, we aim to assess whether EphrinBs in particular are modulated in POMC neurons and whether this modulation can be correlated with number of excitatory inputs into POMC neurons, their excitability and insulin resistance and glucose intolerance.

This project aims to provide novel mechanisms underlying the onset of insulin resistance and glucose intolerance observed in prediabetic conditions, and in particular whether and how POMC neurons could participate to this process.

TANYCYTE/NEURON COMMUNICATION IN THE REGULATION OF ENERGY BALANCE

DALI R.[1], LANGLET F.[1],

University of Lausanne[1]

Energy balance requires the integration of peripheral information by the brain to adjust food intake and energy expenditure in line with the nutritional status of the organism. Hypothalamic tanycytes are essential glial cells for the integration of peripheral cues and the transmission of metabolic information to neurons regulating energy balance. Recently, our group showed that tanycytes make contacts with neurons in the arcuate nucleus of the hypothalamus (ARH), a key nucleus involved in the regulation of energy balance. However, how tanycytes communicate with neurons to transmit metabolic information remains unknown.

Our pilot experiment highlighted Annexin A1 (AnxA1) as a condidate tanycyte signaling molecule modulating hypothalamic neuronal activity and gene expression in response to energy balance. Here, we show that Annexin A1 (AnxA1) is expressed along the third ventricle in the anteroposterior axis, mainly by VMH and DMH tanycytes. Interestingly, mice challenged with a fasting-refeeding paradigm display an increase in tanycytic AnxA1 expression during refeeding. In contrast, AnxA1 expression is decreased in mice fed with a high-fat high-sucrose diet for 8 weeks. Our *in vitro* experiment also demonstrates that AnxA1 expression and subcellular localization are regulated by glucose concentrations. Finally, intracerebroventricular injections of AnxA1 N-terminal active peptide induce cFos cellular activation in the hypothalamic neurons.

Our results suggest that tanycytic AnxA1 expression is regulated by the metabolic and/or inflammatory status and can induce neuronal activation in the hypothalamus. This constitutes a first step in our effort to understand how tanycytes modulate neuronal function and energy balance.

Comparative analysis of the distribution, structure and innervation of Pacinian corpuscles across different mammalian species

Cuenu Velasco A.[1],

University of Geneva[1]

Our ability to sense vibrations depends on diverse mechanoreceptors. Among them, Pacinian corpuscles (PCs) are sensitive to high frequency vibrations. Interestingly, the vibration frequencies with the highest sensitivity seem to change across different mammalian species. Whereas humans show the highest sensitivity around 240Hz, mice are most sensitive around 1000Hz. To understand if this difference in vibrotactile tuning can be related to structural aspects of PCs, we conducted a comparative study of the anatomy, distribution and innervation of PCs in the forelimbs of mice, mouse lemurs and humans.

To determine the distribution and innervation in situ we adapted whole-limb tissue-clearing, immuno-staining and light-sheet imaging methods. We demonstrate that all three species have dense distributions of PCs around the bones of their forelimbs, which are innervated by the anterior interosseous nerve. Unlike both primate species, mice seem to lack PCs in the glabrous skin of their hands. We also observed a difference in overall size and organization of the outer core across species. Whereas in humans the size of PCs ranged from 100 to 1850µm, mouse lemurs and mice showed much smaller PCs (15 to 200µm, and 20 to 100µm). Finally, we found differences in the shape and size of the inner core, and are currently confirming this with full PC reconstructions using electron microscopy.

Although our analysis revealed substantial differences in size and organization of PCs across different mammalian species, more experiments, including single PC electrophysiology, might be necessary to relate these differences to changes in the best frequency tuning observed.

The Representation of Proprioceptive Information by Granule Cells and Climbing Fibers in the Cerebellum

Scheer I.[1],

University of Fribourg [1]

Motor adaptation allows movements to be accurately executed despite perturbations. Proprioceptive re-afferent signals from the limb are used to detect such perturbations. The main target of proprioceptive afference is the cerebellum, which receives proprioceptive inputs via two distinct pathways: the mossy fiber-granule cell (GrC) input from the spino-cuneate tract, and climbing fiber (CF) input from the spino-olivary tract. Both synapse onto the Purkinje cell (PC), where their connections are thought to be the main site of plasticity underlying motor adaptation. To understand how these two input-streams interact and guide motor adaptation, it is essential to characterize what proprioceptive information each encodes.
Accordingly, we imaged GrCs (Math1-Cre x Ai148 transgenic mice) and CF axonal terminals (AAV1-CaMKII-GCaMp7f virus injection in the inferior olive) in the cerebellar cortex with 2-photon microscopy while awake head-restrained mice were subjected to a novel passive forelimb displacement task. The forelimb was passively displaced in an unpredictable manner by a robotic manipulandum in 8 coplanar directions, with varying velocities and amplitudes. We found that most CFs are activated by movements in all directions and that their activity increases with movement velocity, but not amplitude. GrCs, however, are directionally selective and exhibit heterogeneous response properties.
Our findings suggest that CFs allow for flexible tuning of individual PCs by inducing plasticity independently of movement direction: CFs could up- or down-regulate specific signals amongst the rich and precise sensory information conveyed by GrCs. The next step is to understand the mechanism of plasticity by observing how these signals are modified during movement adaptation.

Identification of the local axonal and synaptic translatome in a Drosophila model of Wallerian degeneration

Paglione M.[2], Zakhia S.[1], Terenzio M.[1], Neukomm L.[2],

OIST (Okinawa Institute of Science and Technology Graduate University)[1], University of Lausanne[2]

Sustained integrity of neurons is essential for life-long nervous system function. Neurite morphology and function rely on distinct local mechanisms, and their impairment results in axon and synapse degeneration. However, our understanding of such mechanisms remains incomplete.
Local translation of mRNAs is crucial for axonal and synaptic stability, axon guidance, and regeneration. Therefore, we hypothesize that locally translated mRNAs ensure the homeostasis and integrity of axons and synapses, even in the absence of cell body-derived support. We used a *Drosophila* model based on axonal injury to identify and explore the axonal and synaptic translatome.
We show that an evolutionarily conserved axon death signaling cascade executes the degeneration of severed axons of ~40 labeled sensory neurons within a day upon axotomy. Conversely, axons and synapses with attenuated axon death signaling remain morphologically preserved for weeks *in vivo*. They remain circuit-integrated, as demonstrated by optogenetics coupled with a simple behavior. One week after antennal and maxillary palp ablation, the local translatome was isolated from ~800 sensory neurons through a GFP-tagged ribosomal subunit (GFP::RpL10). The transcriptional profiling revealed approximately 500 differentially enriched transcripts linked to oxidative stress, axon guidance, and transmembrane transport. Further in-depth analyses of the isolated axonal and synaptic translatome will be presented.
Our approach should facilitate the identification of novel axonal mechanisms that locally ensure axonal and synaptic morphology and circuit integrity. It may also reveal novel targets for therapeutic intervention in neurodegenerative diseases.

Autosis-mediated neuronal death: what are the molecular mechanisms?

Depierre P.[2], Ginet V.[1], Truttmann A.[1], Puyal J.[3],

University Hospital Center of Vaud[1], University of Lausanne[2], University of Lausanne, University Hospital Center of Vaud[3]

We previously provided evidence that autophagy (a physiological process of degradation of 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-dependent type of autophagic cell death, in dying CA3 neurons of the hippocampus following perinatal cerebral HI.

Aim: Since neuronal autosis could occur in dying neurons, we are now aiming to understand the mechanisms by which autosis leads to neuronal death. We here investigated two main hypotheses: 1) is-it due to an over degradation of specific proteins and/or organelles? or 2) is-it due to an excessive membrane recruitment for the formation of autophagosomes?

Models: We used neurotoxic doses of the pro-autophagy inducer Tat-BECN1 peptide (5µM) and hypoxic/excitotoxic (KaHx) (6% O_2/kainate 30µM) stimulations to induce autosis in primary cortical neuronal cultures.

Results: Our data suggests that the degradation step of autophagy is not involved in neuronal autosis because the inhibition of the lysosomal activity or the fusion between the autophagosome/lysosome with pharmacological (E64d/PepstatinA and Bafilomycin A1) and genetical (shRNA *stx17,* shRNA *snap29*, shRNA *rab7a*) tools were not neuroprotective. Focusing on autophagosome membrane sources, we identified mitochondria and Golgi Apparatus as potent candidates as both organelles were significantly affected by Tat-BECN1 treatment. However, we also found that neuronal autosis is associated with an increased in golgiphagy but not mitophagy. We are now investigating the hypothesis that mitochondria could be potent sources of membranes for neuronal autosis-enhanced autophagosome formation leading to a detrimental over-recruitment of mitochondrial membrane components.

Conclusion: Our results suggest that elucidating the precise mechanisms by which neuronal autosis is affecting organelles could lead to new neuroprotective targets for the treatment of perinatal asphyxia.

Modulating NAD+ homeostasis in photoreceptor neurons in Drosophila

Kocia M.[1], Neukomm L.[1],

University of Lausanne[1]

Nicotinamide adenine dinucleotide (NAD^+) is an essential coenzyme and cofactor involved in fundamental processes in cells. Low NAD^+ levels are linked to various metabolic and neurological disorders, which can be partially rescued by dietary supplementation or genetic manipulation that maintain NAD^+ homeostasis. However, our understanding of how a decrease in NAD^+ mechanistically results in neurodegeneration is still evolving.

Here, we present a novel *Drosophila* model to modulate NAD^+ homeostasis in photoreceptor neurons. NAD^+ levels are lowered by expressing a constitutively active NAD^+ hydrolase dSarm that lacks its autoinhibitory ARM domain ($dSarm^{\Delta ARM}$). The specific expression of $dSarm^{\Delta ARM}$ in developing photoreceptor neurons triggers their degeneration observed by *in vivo* live-cell imaging. Photoreceptor neurodegeneration results in a striking degenerative rough-eye phenotype in adult flies.

As a proof-of-concept, the sole dietary supplementation with metabolic NAD^+ precursors results in a partial reversion of the rough-eye phenotype. Compounds that target other NAD^+-consuming enzymes result in a similar partial reversion. Likewise, autonomous genetic manipulations of enzymes involved in NAD^+ metabolism also moderately revert the rough-eye phenotype.

We also present our preliminary characterization of mutants isolated in a forward genetic screen that fully revert the rough-eye phenotype. These candidates either stabilize NAD^+ homeostasis or suppress neurodegeneration induced by low NAD^+ levels.

Impaired NAD^+ flux triggers a broad range of metabolic disorders. Evolutionarily conserved genes identified in our *Drosophila* model might provide druggable targets to ensure robust NAD^+ homeostasis in mammals.

Scicloud: a web-based tool to represent and measure medical science output

Lo Giudice Q.[1],

University of Geneva[1]

The number of scientific publications is continuously expanding and provides a tremendous metadata source to identify and predict scientific trends. Most biomedical articles are referenced in Pubmed, a publicly available database that allows automatic retrieval of metadata such as type of publication, date of submission, author credentials, and scientific content (abstract).

To take advantage of these resources, we developed Scicloud, a webpage-based tool that analyzes and represents how researchers publish worldwide and sheds light on a neglected domain of science: the representation of science itself.
We built Scicloud in four steps: (1) parsing and text-mining of the Pubmed public database, (2) inference and integration of geographic information for each entry and each author, (3) indexing and interrogation of the generated knowledge by a search engine strategy and (4) interrogation and display through an interactive world map web page.
We expect that the implementation of this tool will provide opportunities for scientists of all levels of training and for various stakeholders such as private and national funding agencies, editors, and the public at large.

Unravelling the role of atg101 in the brain: generation of the first atg101 knock-in mouse

Daskalaki A.[2], Siva Sankar D.[1], Dengjel J.[1], Nikoletopoulou V.[2],

University of Fribourg[1], University of Lausanne[2]

Atg101 is a core autophagy protein specifically expressed in non-yeast eukaryotes, substituting the Atg29-Atg31 complex. It participates in the ULK1 complex, by directly binding to Atg13 via their HORMA domains. It is indispensable for autophagy initiation under starvation, as it prevents the proteasomal degradation of Atg13 and provides a scaffold for the recruitment of downstream autophagy partners, such as LC3 and WIPI2. However, these studies have been conducted in non-neuronal cells, raising questions on the role of this protein in neuronal physiology and function. To delineate these functions, we have generated the first *atg101* knock-in mouse, where *atg101* gene is flanked by two *loxP* sites and a *3xFlag* and an *Avi-tag* has been inserted upstream of the start codon of *atg101* exon. An initial characterization of these animals implies that, while its gene expression remains unaltered, Atg101 protein levels are negatively affected by the insertion, providing a hypomorph of this protein. Such a small reduction in the protein level is sufficient for aberrant development, as the homozygotes for the tag show smaller body size and weight, limb-clasping and increased vulnerability after the second month of life. By mass spectrometric analysis we identified the interactome of this protein, with Atg13 and FIP200 being highly upregulated, providing thus, a confirmation that the incorporation of Atg101 in the ULK1 complex is not perturbed. A neuronal specific *Cre*-deleter will further enlighten the role of this protein in the brain and clarify its importance for autophagy induction in neuronal cells.

Determination of the Ca2+ binding sites of acid-sensing ion channel 1a (ASIC1a)

Molton O.[1], Bignucolo O.[1], Kellenberger S.[1],

University of Lausanne[1]

Acid-sensing ion channels (ASICs) are Na^+-permeable channels that are activated by extracellular acidification [1]. They are widely expressed in the nervous system and have many physiological and pathological functions such as pain sensation and neurodegeneration after ischemia. ASIC1a is the most abundant subunit expressed in the central nervous system. Calcium ions appear to compete with protons for binding sites of ASIC1a, thereby shifting the pH dependence [2]. Currently, the Ca^{2+} binding site mediating the shift in pH dependence in ASIC1a is not known. A recent study depicting the crystal structure of ASIC1a has shown approximate locations of calcium in two extracellular regions of ASIC1a [3]. This study did however not identify the amino acid residues that coordinate the Ca^{2+} ions and are relevant for the modulation of the pH dependence. Identification of the Ca^{2+} binding sites would tremendously improve the understanding of the activation mechanism of ASIC1a and would help for the design of therapeutics targeting ASIC1a. Based on this structural information [3], Molecular Dynamics simulations have been carried out in our laboratory to refine the calcium coordination, identifying 14 residues that might be part of the calcium binding sites. Site-directed mutagenesis of these predicted amino acids into Alanine was done individually and in combination. ASIC1a WT and mutants were expressed in Xenopus oocytes and two-electrode voltage-clamp measurements in whole-cell configuration were performed 24 h to 72 h after RNA injection. The pH dependence of activation of the WT ASIC1a was measured with 2mM and 100nM of Ca^{2+}, and the shift of the pH values of half-maximal activation (ΔpH50) was calculated by subtracting the pH50 at 2mM from the pH50 at 100nM Ca^{2+}. We tested, whether in mutants, this shift was smaller. We observed a shift toward more alkaline pH50 value by 0.28 pH units with the lower Ca^{2+} concentration condition for the WT ASIC1a. A significant reduction of this alkaline shift was observed for eight mutants localized in two different extracellular regions of ASIC1a. We identified several good candidates for the Ca^{2+} binding sites of ASIC1a. However, the effect of individual mutations on the ΔpH50 was very small. By combining these mutants, we expect to obtain a bigger effect and maybe an abolition of the modulating effects of Ca^{2+}. With this, we hope to establish how the calcium binding sites are related to the effect of calcium on the pH dependence of activation and desensitization.

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Pain

Electrophysiological Profile of Macrophages and Satellite Glial Cells in the Dorsal Root Ganglion after Spared Nerve Injury

Konnova E.[1], Deftu A.[1], Chu Sin Chung P.[1], Decosterd I.[2], Suter M.[1],

CHUV[1], CHUV/UNIL[2]

The spared nerve injury (SNI) is a model of neuropathic pain. Ligating the tibial and peroneal branches of the sciatic nerve, results the development of painful hypersensitivity in the lateral part of the paw that is innervated by the intact sural branch. We hypothesize that macrophages and satellite glial cells (SGC) in the dorsal root ganglion (DRG) contribute to the sensitization of uninjured sural neurons. We aim to characterize the activation state of these cells after SNI.

The number of CX3CR1+ macrophages and GFAP+ SGC increases in the L3 and L4 DRG, where injured and uninjured neurons are present. However, only macrophages express the proliferation marker Ki67. The proteomic profile of macrophages ipsilateral to SNI is significantly different from contralateral macrophages. On the contrary SGC did not reveal expression changes: GFAP+ may be a subpopulation of activated SGC.

Whole-cell voltage clamp recordings of macrophages and SGC were performed in primary culture of dissociated DRG after SNI. SGC had outward currents, that were inhibited by 4AP. Those currents were not different between ipsilateral and contralateral sides. Conversely, macrophages had inward currents, that were inhibited by ML133, which could be attributed to Kir2.1. Importantly, the inward currents were increased in the ipsilateral side. Overexpression of Kir2.1 in primary DRG macrophages recapitulates the large inward currents.

The change in electrophysiological profile correlates with proliferation and phenotypic change in ipsilateral macrophages. Further research aims to determine if modulation of macrophage's Kir2.1 current is sufficient to impact their function in sensitization of uninjured DRG neurons.

Contribution of peripheral neuronal activity to spinal microglial reactivity in chronic pain

Isler M.[2], Kirschmann G.[1], Chu Sin Chung P.[1], Decosterd I.[3], Suter M.[1],

CHUV[1], University of Lausanne / CHUV[2], University of Lausanne/CHUV[3]

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. In the spinal cord, these macrophages of the central nervous system react strongly to nerve injury with morphological changes, proliferation, and release of pro-inflammatory factors. This microglial reactivity has been linked to abnormal peripheral activity coming from primary sensory neurons (PSN). Indeed, previous studies in rats demonstrated that a preventive block of electrical activity from nociceptive and non-nociceptive PSN after nerve injury is sufficient to prevent microglial reactivity and pain and that electrical stimulation of PSN per se induces spinal microglial activation. In particular, it was shown that electrical activity from nociceptive C fibers is necessary to trigger spinal microglial reactivity. However, it is still unclear whether spinal microglial activation depends on nociceptive C fibers inputs alone or if a combined activity from nociceptive and non-nociceptive PSN is required. Thus, our goal is to further investigate the contribution of nociceptive and non-nociceptive inputs to spinal microglial reactivity in the context of chronic pain. To address this question, we first replicated electrical stimulation on the sciatic nerve in CX3CR1-eGFP mice and could observe increased microglial reactivity in the spinal cord. Then, we used optogenetic tools to selectively activate nociceptive fibers in SNS-ChR2-TdTomato mice and showed that this is sufficient to induce microglial reactivity in the spinal cord.

Sleep

Impact of transcranial alternating current stimulation during a nap on sleep-dependent motor memory consolidation: a behavioral and electrophysiological study in healthy older adults.

Moyne M.[1], Durand-Ruel M.[2], Salamanca-Giron R.[2], Park C.-h.[2], Sterpenich V.[1], Morishita T.[2], Hummel F.[2],

University of Geneva[1], École Polytechnique Fédérale de Lausanne [2]

With the increase in life expectancy, the population of people aged 60 years and older is estimated to rise. Healthy aging is paralleled by a reduction of learning capability that is partially attributable to changes in sleep physiology, specifically sleep oscillations such as spindles. There is growing evidence showing that sleep-dependent memory consolidation and spindles diminish with age. Indeed, the association between spindles and motor memory consolidation is different in young and older adults. Non-invasive brain stimulation (NIBS) has shown potential for memory enhancement when applied during sleep. However, transcranial alternating current stimulation (tACS)—a type of NIBS—targeting spindles has never been applied in healthy older adults. By applying tACS resembling spindles (spindle-inspired tACS) during a nap we aimed to enhance sleep-dependent motor memory consolidation.

Twenty-six healthy older participants (>60yo) are enrolled in this randomized, double-blind, sham-controlled, parallel design study. Motor training consists of 4 sessions: participants perform a training session of a motor gripper task at 10 am and are retested later at 4:30 pm, and 24h post-training. With a gripper device in their left hand, they are instructed to reach targets as fast and accurately as possible by pressing and releasing the gripper in a self-paced fashion. After the training, they have a 90 min opportunity to take a nap under polysomnography monitoring while spindle-inspired tACS is applied (verum) or only one burst of stimulation is applied (sham). To evaluate sleep-dependent motor memory consolidation we calculated offline learning, which is the difference between pre-sleep and post-sleep motor accuracy scores.

The present study reveals that spindle-inspired tACS neither enhanced offline learning nor spindles. The association between spindles and offline learning in the sham group reveals that spindles play an important role for sleep-dependent motor memory consolidation. Yet this association is not observed in the verum group. Therefore, our results indicate that the spindle-inspired tACS seems to perturb the role of spindles for sleep-dependent motor memory consolidation and that future studies might preferentially apply spindle-inspired tACS temporally synchronized with spindles to enhance sleep-dependent memory consolidation in healthy older adults.

A role for interoceptive vGluT2-expressing neurons in the nodose ganglion of the left vagus nerve in the regulation of sleep architecture and spectral composition

Cherrad N.[2], Osorio-Forero A.[2], Cardis R.[2], Emmenegger Y.[2], Arnold M.[1], Franken P.[2], Lüthi A.[2], Fernandez L.[2],

ETH Zürich[1], University of Lausanne[2]

When awake, we consciously perceive stimuli from the world that surrounds us. When asleep, our brain disconnects from the sensory environment. In contrast to these exteroceptive stimuli, little is known about how interoceptive stimuli are processed by the sleeping brain. The vagus nerve is a mixed sensory-motor nerve that interfaces between the autonomic periphery and the central nervous system. We asked whether stimulating specifically vagal sensory afferents modulates sleep.

All experiments are based on viral transfection techniques to enable chemo- or optogenetic activation of vGluT2-expressing neurons in the nodose ganglion of the left vagus nerve, in combination with polysomnographic, local field potential (LFP), fiber photometry in freely moving conditions after low (1.5mg/kg i.p.) or high (2.5mg/kg i.p.) CNO injections or NaCl at ZT0.

Whole-cell patch-clamp recordings confirmed that optogenetic activation of vagal afferents formed functional glutamatergic synaptic contacts in the brainstem nucleus tractus solitarius. In a next step, we found that chemogenetic activation of the vagal sensory afferents suppresses rapid-eye-movement sleep (REMS) in its major spectral and autonomic correlates. The REMS onset latency was increased from 13±2min after NaCl injection to 82±16min after low-dose (Wilcoxon-sign-rank-test, p=4.8e-4, n=11) to 185±27min after high-dose CNO injection (Wilcoxon-sign-rank-test, p=2.4e-4, n=11). Moreover, heart rate remained decelerated throughout the period during which REMS was not detectable. In contrast to the suppression of REMS, the spectral properties of non-REMS were moderately affected, with evidence for a minor increase in low-frequency power (delta (1.5-4Hz) (n=11, p=1.8e-4, Student's-t-test) and slow oscillations (0.5-1.5Hz) (n=11, p=6.6e-4, Student's-t-test)) and a decrease in spindle power (10-15Hz) (n=11, p=1.5e-4, Student's-t-test) after a low dose of CNO. To characterize more comprehensively the physiological correlates of sleep during elevated vagal activity, we are currently analyzing breathing rates and the cortical temperature. The mechanisms underlying these alterations are addressed using fiber photometry techniques in combination with LFP recordings.

Our findings point to a major role for vagal afferent activity in body-brain physiology that regulates the balanced expression of non-REMS and REMS. Moreover, they indicate that vagus nerve stimulation could offer non-invasive strategies to improve sleep architecture in pathological conditions.

Cardio-audio and auditory regularity encoding during human wakefulness and sleep

Pelentritou A.[1],

University of Lausanne[1]

The human brain can implicitly encode temporal regularities across cardiac and auditory inputs. We investigated whether cardio-audio regularity processing occurs during sleep, when the balance between bodily and environmental stimulus processing may be altered. Using electroencephalography (EEG) and electrocardiography (ECG) in 26 healthy volunteers during wakefulness and sleep, we measured the response to unexpected sound omissions within three regularity conditions: synchronous, where sound and heartbeat were temporally coupled, isochronous, with fixed sound-to-sound intervals, and a control condition, asynchronous, without specific regularity. Cluster permutation statistical analysis ($p<0.05$, two-tailed) contrasted the EEG omission responses across experimental conditions and revealed a modulation of the omission-evoked neural response induced by the synchronous and isochronous sequences in wakefulness (at 226-274ms after heartbeat onset and 226-288ms after omission onset, respectively) and N2 sleep (at -99-117ms and 322-500ms and 83-226ms, respectively). The same auditory sequences resulted in reorganization of background oscillatory activity in N2 sleep, observed as a difference in the median sound to SO latencies across auditory conditions, with higher latencies in the asynchronous condition ($p<0.05$) compared to the synchronous and isochronous conditions. Cardio-audio regularity encoding was further demonstrated by a heartbeat deceleration upon omissions in all vigilance states, uncovered by comparing ECG-derived interbeat intervals across auditory conditions, outlining higher omission interbeat intervals in the synchronous compared to the other regularity types ($p<0.05$). Humans process cardio-audio temporal relationships to predict future auditory events across distinct vigilance stages.

Acot11 links lipid metabolism and sleep wake regulation

Dukanovic N.[1],

University of Lausanne[1]

Insufficient and disrupted sleep is a serious public concern. Clinical studies associate loss of sleep with the increased risk of developing metabolic disorders, i.e. obesity and type-2 diabetes. Using the system genetics approach in mice, the liver expression of *Acyl-CoA Thioesterase 11* (*Acot11*), an enzyme involved in lipid metabolism, was associated with NREM sleep recovery after sleep deprivation (SD) (Diessler, Jan. 2019). Moreover, circulating long-chain phosphatidylcholines were linked with both the -Acot11 expression and NREM sleep recovery. ACOT11 regulates energy expenditure in energy-demanding tissues and ACOT11 KO mice show resistance to developing metabolic disorders, e.g. insulin resistance. Hence, we aim to investigate the functional role of *Acot11* as a link between sleep recovery and metabolic dysregulation upon SD using a KO mouse model. EEG analyses revealed a difference in sleep recovery after SD, specific for the NREM sleep in the last 6h of the dark period (ZT 18-24), when KO mice experience NREM sleep recovery loss. Although the sleep duration differed between genotypes, the quality of sleep was preserved. Metabolomic analysis of lipids and carnitines species in the liver, brain cortex and blood revealed significant genotype effects on the plasma membrane-associated phospho- and sphingolipids, whereas sleep deprivation had a significant effect on the triglyceride species in liver and blood plasma, linked to the lipid storage. To further elucidate the role of *Acot11* as a link between disturbed sleep and deregulated metabolism we will perform the transcriptomic analysis and the additional metabolic phenotyping.

SomnoLux: Pupillometry, perception and cognitive function in sleep

Novozhilova S. , Yesica Gloria, Christina Zavlanou, Laurence Bayer, Guillaume Legendre, Lampros Perogamros, Ozge Yuzgec, Sophie Schwartz, Daniel Huber

Department of Basic Neurosciences, University of Geneva

One of the most effective treatments of anxiety disorders is exposure therapy. This involves the gradual approach of exposing the patient to feared situations in a safe setting, thereby helping to overcome their distress by extinction learning. Sleep seems to play a key role in the consolidation of this type of memory. But what if the actual exposure therapy was carried out directly during sleep? Previous studies used associations with auditory or odor cues to indirect exposure, but with limited success. What if specific visual cues or images were presented directly to sleeping subjects? Would this be more effective? The SomnoLux system uses pupil and gaze tracking combined with closed-loop visual stimulation techniques, which allows participants to sleep comfortably with their eyes open. By doing so, we aim to investigate the links between pupil dynamics, brain activity, perception and cognitive function in sleep with the goal to inform the conception of a therapeutic technique involving visual stimulation during sleep. We have developed a sleep-compatible virtual reality (VR) headset allowing for reliable eye tracking and safe presentation of visual stimuli during sleep. Coupling our visual stimulation paradigm with polysomnography we can examine well defined biomarkers of cortical processing and arousal via electroencephalography (EEG) and eye tracking.
The first series of pilot experiments employ the VR headset in passive image viewing paradigms during the entirety of a sleep session. Our findings compare responses measured with EEG during wake and during sleep. Results show how different brain states affect visual processing. The presentation of a visual stimulus successfully evokes a visual evoked potential (VEP) across all stages of sleep. Additional findings of an oddball experiment suggest the possibility of evoking an attentional event related potential (ERP) the P300. Taken together, our pilot experiment results shine light on the potential visually salient cognitive functions that remain active during sleep.

Role of the hydroxycarboxylic acid receptor 1 (HCAR1) in hippocampal network regulation during epileptic seizures.

Alessandri M.[1], Osorio A.[1], Cardis R.[1], Lüthi A.[1], Chatton J.-Y.[1],

University of Lausanne[1]

Epilepsy is the most common neurological disorder, with about 50 million people suffering from this disorder. Here we aim to study the role of the lactate receptor hydroxycarboxylic acid receptor 1 (HCAR1) in regulating the hippocampal network in the pathology of epilepsy and its ability to modulate seizures. HCAR1 is significantly enriched in the hippocampal glutamatergic neurons in the CA fields and the dentate gyrus. Investigations first using mouse primary neuronal cultures and then acute brain slices led us to unravel the mechanisms of action of HCAR1 as a modulator of neuronal activity and its interactions with other Gi-protein coupled receptors involving Gβγ subunits. By its ability to reduce neuronal activity and its expression by glutamatergic hippocampal neurons, HCAR1 appears as a potential target for the modulation of seizures. In this study, we focused on the pathophysiology of acute seizures. We elicited seizures on freely behaving mice using the intrahippocampal kainate injection model in the presence or absence of the non-metabolized HCAR1 agonist 3-chloro?5-hydroxybenzoic acid (3Cl-HBA) and investigated the potential modulatory effect of HCAR1 activation on seizures using electroencephalography (EEG). We quantified the frequency bands power of delta, theta, alpha, beta, and gamma waves. Contrasting to ex vivo observation by other groups and us, activating HCAR1 during seizures had no significant effect on the recorded signals. We are currently using in vitro models of epilepsy to determine if and under which conditions HCAR1 activation can modulate seizures, with particular attention to potential interference with other Gi-coupled receptors. Our work is a significant step towards understanding lactate in the regulation of hippocampal circuits in epilepsy.

Multi sequence in MRI

Arslan M.[1],

University of Geneva[1]

Magnetic resonance imaging (MRI) one of the most used imaging modalities for assessing, diagnosing, and planning the treatment for diseases. It is a multiparametric imaging modality by nature owing to the large number of MR sequences and contrasts that can be generated. On the other hand, there are some several restrictions of multisequence imaging such as long scanning time for some sequences like T2, Flair compared to T1 and other restriction is the potential allergic hazard for some patients in case of using contrast matter. In this study, we propose to generate T2, Flair and T1 contrast-enhanced, T2 contrast-enhanced images by using ResNet. We split dataset into 1000 brain MR images for training and 251 brain MR images for test and validation. In case of generating T1 contrast-enhanced image by using T1 weighted image, we got 0.9597±0.019 SSIM (Structural Similarity Index Measure) score and in the case of generating T2-weighted brain MR image by using T1-weighted brain MR image, we got 0.961±0.0284 SSIM score. This study still continue to synthesis other sequences. When we look at the preliminary outputs, they have visually and quantitatively good results. After the synthesising other sequences, we will continue to lesion segmentation on synthetic data, finding type of lesion and survival rate of the patient from synthetic data.

Honesty is predicted by moral values and economic incentives but not by acute stress

Sooter N. & Ugazio G.

University of Geneva[1]

Honesty is vital for proper institutional, economic, and societal functioning and compliance with this moral imperative often requires trade-offs between acting honestly and increasing personal gain through cheating. Experimental studies have demonstrated that individuals who hold honesty as a protected value are less inclined to give in to selfish temptations, even in the face of increasing financial motivation. However, while everyday decisions on honesty frequently take place in highly stressful situations, we have little knowledge on whether they are influenced by stress. Stress is known to alter behavior by enhancing neural sensitivity to immediate rewards, promoting habitual behavior, and decreasing activity in brain areas involved in response inhibition and goal selection. Thus, stress could potentially affect honesty by: 1) making monetary rewards more attractive and 2) inducing habitual behavior by reducing self-control. We explored these potential mechanisms by acutely stressing participants and asking them to make decisions in three tasks measuring honesty. Consistent with previous studies, we found that protected values for honesty and the magnitude of rewards associated with cheating were good predictors for honesty, and that higher protected values decreased susceptibility to rewards. In addition, we found Bayesian evidence that acute psychological stress does not impact individuals' subsequent propensity to act honestly.