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Organizing Committee:
Camilla Bellone, Alan Carleton, Anthony Holtmaat and Daniel Huber
@ CMU Geneva

Coordination: Marta Bellone & Ulrike Toepel
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Investigating the role of the serotonin receptor 3A in mPFC microcircuit function during fear extinction

Zewdie S.1, Stefanelli T.1, Mendez P.1, Michel C.1, Quairiaux C.1

UNIGE-CMU1

In humans, early-life stress modifies the methylation status of the serotonin 3a receptor (Htr3a) and interacts with a functional single nucleotide polymorphism in the Htr3a promoter region to modulate stress-related phenotypes. The HTR3A is a cation selective ionotropic receptor specifically expressed in a subset of interneurons distributed in several limbic brain regions including the medial prefrontal cortex (mPFC), a key region regulating fear extinction. Htr3a-ko mice display normal fear acquisition, but fail to extinguish learned fear. In a first set of experiments, we performed intra-cortical electrophysiological recordings in head-fixed wild-type and Htr3a-ko mice and analyzed local field potentials in the mPFC. Preliminary data indicate increased power in the theta range (4-8Hz) specifically in the prelimbic mPFC of Htr3a-ko mice, suggesting that HTR3A+ cortical INs regulate mPFC theta oscillations. As a next step, we aim to determine whether HTR3A-mediated serotonin transmission on specific subsets of mPFC interneurons is required for fear extinction. To do this we have designed a fear extinction protocol in the head-fixed condition and aim to assess brain oscillations and single units in control and Htr3a-ko mice, while measuring pupil dilatation as a behavioral correlate of fear extinction. In addition, we aim to assess the role of HTR3A+ interneurons in fear extinction by using optogenetic manipulations in the mPFC of Htr3a-Cre mice. Overall, this project will provide new insights on the role of the HTR3A in mPFC function during a fear extinction paradigm.
A neuronal circuit for the response to hypoglycemia in the insular cortex

De Araujo Salgado I.1, BenFredj N.1, Lamy C. 1

UNIFR1

Given the importance of glucose for the brain, the glycemic level is highly monitored by the central nervous system. A drop in blood glucose level triggers vital behavioral changes to insure survival. Using whole-cell recording, we have previously identified the existence of glucose-sensing cells in the insular cortex (IC), a region involved in interoception and adaptive behaviors. We are now investigating the neuronal circuit associated with those neurons and their behavioral function. Using a transgenic activity reporter mouse model, we confirmed the presence in IC of hypoglycemia-activated neurons in vivo. We then investigated the role of those neurons in adaptive behaviors by re-activating them in vivo. Our study demonstrates the existence of a neuronal circuit in IC implicated in behavioral adaptation to hypoglycemia.
Imaging of plasticity in the mouse medial prefrontal cortex in a fear conditioning paradigm

Kiss-Bodolay D.\textsuperscript{1}, Fossati G.\textsuperscript{1}, Dayer A.\textsuperscript{1}, Holtmaat A. \textsuperscript{1}

UNIGE - CMU\textsuperscript{1}

Early-life and prolonged stress may cause anxiety states in adults that are maintained as a result of failed fear extinction. This might be the result of maladaptive and persistent plasticity in brain circuits that modulate fear responses such as the medial prefrontal cortex (mPFC). Interestingly, this part of the cortex is highly innervated by the serotonergic system that is widely targeted for pharmacological treatment of these disorders.

In the current project we aim at identifying structural and functional changes in mouse mPFC circuits in response to fear learning, fear extinction, and maladaptive fear responses. Ultimately, we will investigate the role of serotonergic mPFC afferents in these processes.

Using 2-photon laser scanning microscopy, we image neuronal activity and synaptic structures in the mPFC of mice that undergo a fear-conditioning paradigm, spanning the phases of fear learning, expression and extinction. We have adopted a method based on the surgical implantation of microprisms to obtain access to the deeper regions of the mPFC, such as the anterior cingulate and prelimbic areas. We have developed a preparation that can be utilized for long-term imaging of synaptic structures and activity over days to weeks.

We are currently tracking dendritic spine dynamics in GFP-expressing L5 and L2/3 pyramidal neurons, and Ca2+ responses in GCAMP6-labeled L2/3 pyramidal cells. In the future, we aim at investigating the effects of chemogenetic and optogenetic modulation of serotonergic projections on fear learning and extinction as well as neuronal plasticity in the mPFC.
**Microendoscopic imaging of functional responses of claustrum projection neurons during behaviour**

Huber C.

UNIGE - CMU

The claustrum (CLA) is a thin sheet of gray matter that is highly interconnected with the neocortex. Presently, though the CLA has been hypothesized to be involved in conscious perception of sensory stimuli, little is known about its actual function. Here we use a transgenic mouse in which a cre recombinase is expressed in glutamatergic neurons of the claustrum. Using cre-dependent adeno-associated virus, we forced the expression of the genetically encoded calcium indicator GCaMP6f. Using a microendoscope implanted above infected CLA neurons, we imaged calcium responses in freely moving mice during various behavioral conditions. We report that various ensembles of neurons are recruited during different behavior such as open field locomotion and attentional set-shifting tasks. Interestingly, we observed remapping of task representation in couple of trials associated to new rule learning. In conclusion, we report for the first time functional responses of CLA neurons during various behavioral context and our data suggest that multiple specific cell assemblies are recruited during complex behavioral tasks.
Closed-loop Targeted Memory Reactivation in a Slow Wave Up-state Enhances Vocabulary Memory

van Poppel E.¹, Göldi M.¹, Rasch B.¹, Schreiner T. ²

Donders Institute for Brain, Cognition and Behaviour, Radbou University Nijmegen², University of Fribourg¹

It is assumed that the memory function of sleep relies on the spontaneous reactivation of newly acquired memories. Those spontaneous reactivation processes are driven by the cortical slow waves (SW), while inducing memory reactivations by re-exposure to learning-associated memory cues (targeted memory reactivation, TMR) results in enhanced memory performance. Slow waves consist of alternating phases of periods of increased neural firing (up-states) and widespread neural silence (down-states). As the benefits of cued reactivation during sleep might depend on periods of increased neural firing, we hypothesised that cueing foreign vocabularies during SW up-states would lead to enhanced recall performance, speaking for the crucial role of SW up-states in the reactivation of memories.

Native German speakers learned 120 Dutch-German word-pairs in the evening. During subsequent NonREM sleep, SW’s were detected online. 1/3 of the prior learned words were repeatedly presented during SW up-states, 1/3 during down-states and 1/3 not at all. After three hours of night-time sleep, the word knowledge was tested using a cued recall procedure.

Words replayed during SW up-states benefited the most as compared to uncued. Still, down-state replayed words benefited as well but to a lesser degree than the up-state replayed words.

Replaying words during the SW up-state phase is related with the strongest memory enhancing effects, suggesting that TMR is more likely to be processed during this up-state. TMR is more variable when the reactivation occurs outside of the up-state. Future analyses will aim for characterizing what makes cueing beneficial the most.

Abstract # 5
Neural substrate of sound object segregation

Tissières I.¹, Crottaz-Herbette S.¹, Spierer L.², Clarke S.¹

CHUV¹, UNIFR²

Dissociation between deficits in explicit sound localization and in sound object segregation on the basis of spatial cues was reported in previous studies, suggesting the existence of a position-linked representation of sound objects that is distinct from the position-independent representation within the ventral auditory stream and from the explicit sound localization processing within the dorsal stream. Here we provide evidence for the anatomical substrate of spatial-cue based sound object segregation.

Fifty-seven participants (17 controls; 20 patients with left and 20 with right hemispheric damage) were assessed for sound localization and for spatial release from masking (SRM). The latter used two simultaneous environmental sounds; position of the masker varied (a central and 2 positions within each hemispace) whereas target remained central. Voxel-based Lesion-Symptom Mapping (VLSM) was applied to either task.

Performance in the localization task depended critically on the right parietal cortex, confirming the role of the right dorsal pathway in explicit localization.

For the SRM, separate VLSM analyses were performed for each masker positions. It highlighted the critical role of a large temporo-parieto-frontal region within the left hemisphere, independently of the position of the masker. In addition, a smaller parieto-temporal region was highlighted, more specifically when the masker was central or to the right.

Thus, explicit sound localization and implicit use of spatial cues for sound object segregation depend on at least partially distinct neural networks. These findings are in agreement with a previous EEG study on the role of a left temporo-frontal network in position-linked representation of sound objects.
A neuroanatomical model of space-based and object-centered processing in spatial neglect

Pedrazzini E.¹, Schnider A.², Ptak R.³

UNIGE_HUG², UNIGE - HUG¹, UNIGE-HUG³

Visual attention can be deployed in space-based or object-centered reference frames. Right-hemisphere damage may lead to distinct deficits of space- or object-based processing, and such dissociations are thought to underlie the heterogeneous nature of spatial neglect. Previous studies have suggested that object-centered processing deficits (such as in copying, reading or line bisection) result from damage to retro-rolandic regions while impaired spatial exploration reflects damage to more anterior regions. However, this evidence is based on small samples and heterogeneous tasks. Here, we tested a theoretical model of neglect that takes into account the space- and object-based processing and relates them to neuroanatomical predictors. One hundred and one right-hemisphere damaged patients were examined with classic neuropsychological tests and structural brain imaging. Relations between neglect measures and damage to the temporal–parietal junction, intraparietal cortex, insula and middle frontal gyrus were examined with two structural equation models by assuming that object-centered processing (involved in line bisection and single-word reading) and space-based processing (involved in cancelation tasks) either represented a unique latent variable or two distinct variables. Of these two models the latter had better explanatory power. Damage to the intraparietal sulcus was a significant predictor of object-centered, but not space-based processing, while damage to the temporal–parietal junction predicted space-based, but not object-centered processing. Space-based processing and object-centered processing were strongly intercorrelated, indicating that they rely on similar, albeit partly dissociated processes. These findings indicate that object-centered and space-based deficits in neglect are partly independent and result from superior parietal and inferior parietal damage, respectively.
Illusory contours (ICs) have been extensively studied, as they simulate mid-level vision processes. ERP correlates of ICs sensitivity were found at ~100-150ms post-stimulus onset. It is well-established that multisensory processes can influence both low-level vision, as well as higher-level object recognition. It is unknown if mid-level vision benefits from auditory inputs. This would be important, given evidence for impaired IC perception in sight-restored individuals after cataract removal who nonetheless present clinically normal vision. We reasoned that sounds would impact completion processes supporting IC sensitivity. Participants viewed arrays of black pacman inducers on a dark grey background that were oriented to form ICs or no-contour (NC) counterparts in a 2x2x2 within-subject design. Two varieties of inducers were used to differentiate potential effects of sounds on completion processes as opposed to more general brightness enhancement of the inducers; that occurs for modal, but not amodal inducer stimuli. An uninformative sound was presented on half of the trials. Participants indicated IC presence vs. absence while 128-channel EEG was recorded. IC sensitivity was enhanced by uninformative sounds; there was a significant interaction between IC/NC and sound presence at ~150ms post-stimulus onset. The 3-way interaction was significant only at ~300ms, suggesting that the effect of sounds on IC sensitivity at ~150ms was indistinguishable across both modal and amodal completion. Our findings significantly extend prior work documenting the presence of multisensory interactions during early stages of stimulus processing by indicating that multisensory interactions can facilitate mid-level vision and may thus be a strategy for visual rehabilitation.
A preclinical model for identifying rats at risk of alcohol use disorder

Jadhav K., Magistretti P., Halfon O., Augsburger M., Boutrel B.

Toxicology and Forensic Chemistry Unit, University Center of Legal Medicine, Center for Psychiatric Neuroscience, Department of Psychiatry, Lausanne University Hospital, Division of Adolescent and Child Psychiatry, Department of Psychiatry, Lausanne University Hospital, King Abdullah University of Science and Technology (KAUST), Thuwal, Saudi Arabia, CNP/CHUV

Aims:
Unhealthy alcohol use is one of the world’s leading causes of death and disease. Though, only a small proportion of individuals develop persistent maladaptive alcohol intake. Here we propose a novel approach to identify rats exhibiting high risks of losing control over alcohol intake according to a preclinical model we adapted from that of Deroche-Gamonet et al., Science, 2004.

Method:
Inter-individual vulnerability to alcohol abuse has been evaluated in rats daily trained for 80 days by modeling the operational definitions of DSM criteria: 1) an inability to abstain from alcohol seeking during signaled periods of reward unavailability, 2) an increased motivation to consume alcohol assessed in a progressive effortful task and 3) persistent alcohol taking despite aversive electrical foot shocks.

Results:
Factor analysis showed that the three addiction criteria loaded on one underlying construct. We clubbed together rats with negative in contrast to rats with positive addiction traits for further analysis. Not only the addiction trait positive group exhibited higher ethanol consumption by the end of the daily training, and higher preference for ethanol over sweetened solutions and even water, but it also exhibited pre-existing higher anxiety and impulsive traits as compared to the addiction trait negative group.

Conclusion:
This preclinical model confirms that addiction like trait develops in a small proportion of individuals exposed to ethanol. Further, this development not only requires prolonged exposure to alcohol but also depends on individual vulnerabilities or endophenotypes that predispose individuals to lose control over alcohol consumption.
APOE*E4-related effect on the topological brain network attributes in Mild Cognitive Impairment: A three-year follow-up study

Sanabria Diaz G.¹, Draganski B.¹, Melie Garcia L.¹, Kherif F.¹

CHUV¹

The apolipoprotein E ?4 allele (APOE*E4) has been consistently associated with a higher risk of developing late-onset Alzheimer’s disease (LOAD). Previous studies in Mild Cognitive Impairment (MCI), considered a disease prodromal phase, have reported increased risk of LOAD progression and rapid cognitive decline in APOE*E4 carriers. However, inheriting the allele does not mean that MCI patients will definitely develop Alzheimer’s. In the present study, we investigated how APOE*E4 status modulates the topological organization of structural brain networks in MCI depending on their clinical progression. We used graph theory and cortical thickness obtained from 762 T1-weighted structural magnetic images to study brain network properties during a 3-year follow-up period. The sample comprised 64 APOE*E4-positive (?carriers’) MCI and 63 APOE*E4-negative (?non-carriers’). The groups were stratified into converters and non-converters. All subjects were selected from the ADNI database. The co-variation patterns among anatomical regions showed the double of differences in MCI carriers converters compared to non-converters. Large co-variations patterns differences between these groups involved structures like inferior parietal cortex and precuneus described previously as a core of regions highly connected. The MCI carrier’s converters showed a significant increase in characteristic path length, clustering index, local efficiency, global connectivity and a global efficiency decrease. However all these measures were significant lower compared to carriers non-converters. Others topological properties like target attack and modularity indicated an aberrant network organization in MCI carrier’s converters over time. Our findings suggest that whole-brain topological attributes could improve prediction of LOAD conversion in MCI APOE*E4 positive.
Semantics in the multisensory brain: Insights from electrical neuroimaging

Turoman N.¹, Tivadar R.¹, Murray M.¹, Matusz P. ¹

CHUV¹

Successful integration of multisensory information into a unified object is dependent on both lower-level factors (e.g., simultaneity), and higher-order factors (e.g., semantic congruence). The brain and cognitive mechanisms that govern the latter remain unclear. Among the scant studies of multisensory semantic congruence in existence, most have not controlled for simultaneity detection or the task-relevance of simultaneity and/or semantic congruence. Nevertheless, there is evidence that semantic congruence impacts multisensory stimulus processing independently of top-down attention, such that memory benefits from prior exposure to semantically congruent multisensory contexts. In the present study, healthy adults performed a continuous “old/new” task involving sounds of naturalistic objects while 64-channel EEG was recorded. On initial presentations, each sound was accompanied by a semantically congruent (AVc) or meaningless drawing (AVm) or appeared alone (A). Repeated presentations were exclusively sounds. Categorising a sound as “new” benefited from multisensory semantic congruence (AVc), but not mere simultaneity (AVm). ERP analyses revealed topographic differences between AVc and AVm, at 184-256ms. Over this latter period (208-262ms) one topographic map predominated responses to AVc, while multiple maps characterised responses to AVm. Responses to AVc were stronger and peaked earlier than those to AVm (224-270ms). Brain networks responsive to multisensory semantic congruence are thus distinct from those responsive to multisensory simultaneity. Moreover, memory benefits from task-irrelevant semantically congruent multisensory contexts are accompanied by predominance of activity of one brain network >200ms post-stimulus onset. These results support recent theoretical frameworks characterising the interplay between attention and memory by highlighting their role in orchestrating multisensory processes.
Neural correlates of reality filtering in psychosis

Thézé R.¹, Manuel A.¹, Pedrazzini E.¹, Chantraine F.², Patru C.², Nahum L.², Guggisberg A.², Schnider A. ²

HUG², UNIGE - HUG¹

Psychosis is characterized by symptoms of hallucinations and delusions, which reflect a difficulty in distinguishing what does not pertain to reality. Orbitofrontal cortex (OFC) lesions also induce a confusion of reality, as evidenced by patients acting upon their confabulations and by disorientation. The mechanism normally verifying whether an upcoming thought relates to ongoing reality, or not, is called “orbitofrontal reality filtering” (ORFi). It is observable from repeated runs of a continuous recognition task and is characterized in healthy subjects by a frontal potential at 200-300 ms originating from the OFC. Here we explored whether the reality confusion in psychosis was also associated with disturbed ORFi. We recorded high-density electroencephalography (EEG) from 17 patients diagnosed with mild to severe psychosis (Brief Psychiatric Rating Scale, v.4) matched with healthy controls while they performed two runs of the aforementioned continuous recognition task. Patients group, compared to controls, performed equally well at the recognition task and displayed a significantly reduced, although present, frontal potential between 200-300 ms. This reduction was predictive of psychosis. There were no differences in OFC activation but rather increased local activity in medio-temporal and prefrontal regions in patients. Functional connectivity analysis furthermore demonstrated that interregional oscillations in the theta-band frequency were completely disturbed in patients between regions of the memory network, all directly or indirectly connected. These findings suggest reality perception in schizophrenic patient is affected by aberrant functional connectivity in the memory network, although ORFi is partly compensated.
When pain appraisal is not based only on the patient. The role of feedback-based learning in medical environment

Dirupo G.¹, Totaro S.¹, Corradi-Dell'Acqua C. ¹

UNIGE - FAPSE¹

Medical practitioners often underestimate others’ pain, sometimes disregarding patients’ self-reports. We explore whether this effect can be explained through the processes of feedback-based learning, according to which individuals adjust their behavior depending on previous feedback about their own performance. Medical students and controls watched videos of facial expressions and rated the associated pain. Subsequently, they were exposed to two feedback cues, independently manipulated for their social and informational significance. In particular, cues could represent the self-report of the video’s protagonist, or the average judgement of 20 emergency doctors on the same expression (social dimension). Furthermore, cues reported different degrees of pain, with one describing more pain than the other (informational dimension). 30 minutes later, participants were unexpectedly required to rate the same expressions.
We analyzed whether participants changed their response in the second session as function of the feedback cues. We found that participants were sensitive to the social dimension of the cues, as they conformed to the protagonist self-report, without any reliable group difference. Moreover, medical students and controls differed in the degree with which they processed the informational dimension of the cues: controls were influenced by cue signaling the highest pain while medical students adapted their rating as function of the cue signaling the lowest pain. This effect was observed only on experienced medical students (> 4th year of university), not in younger ones.
Our data reveal how medical education affects feedback-based learning of pain appraisal, by leading medical practitioners at weighting more conservative feedback.
Sleep structure and quality in mouse models of chronic pain

Cardis R.

Unil/CHUV

One of the major complaints in chronic pain patients are sleep disturbances. Patients complain experiencing disrupted sleep and fatigue during the day. In turn, non-reparative sleep increases pain sensitivity. The bidirectional interaction between sleep and pain is poorly understood. We use the well-described spared nerve injury (SNI) mouse model of chronic pain to monitor sleep architecture and spectral profile as pain evolves over weeks, using polysomnography recordings in normal light/dark conditions (n = 6). Sleep stages were scored and quantified over 5 sessions of 48 h, prior to and until four weeks after SNI or sham surgery. During the light phase, SNI mice showed minor changes in sleep time post-surgically (~3 % more NREMS) and mean NREMS bout duration was prolonged (SNI ~125 s, Sham ~95 s), suggesting better sleep consolidation. The declining time course of delta power during the light, an index of recovery from sleep pressure, seemed also preserved. In contrast, in the early active phase, delta power increased ~1.2-fold more strongly in SNI animals at 4 weeks post-surgery. Thus, SNI animals have either difficulties entering sleep in this period or their waking produces greater fatigue. The accumulated sleep duration showed that SNI progressively gain sleep during the light phase, yet lose it in the first half of the dark phase.

These findings suggest that chronic pain largely preserves sleep during the resting phase, but augments the development of sleep pressure during waking. In a next step, we will address the sleep regulatory mechanisms and some of the neural circuits involved in this pain-driven sleep disturbance.
Peripheral administration of Lactate produces antidepressant-like effects

Carrard A.¹, Elsayed M.², Margineanu M.³, Boury-Jamot B.¹, Fragnière L.¹, Meylan E.¹, Petit J.-M.¹, Fiumelli H.³, Magistretti P.³, Martin J.-L.¹

EPFL/LNDC², CNP/CHUV², KAUST³

As clinical and basic research studies have shown that major depression and chronic stress are associated with alterations in structural and functional plasticity and as evidence supports a role for L-lactate as an intercellular signaling molecule involved in synaptic plasticity, we investigated the role of L-lactate as a potential novel antidepressant.

We found that peripheral administration of L-lactate produced antidepressant-like effects in the forced swim test. The antidepressant response induced by acute L-lactate administration was accompanied by increases in hippocampal L-lactate concentration and by changes in GSK3β/α and CREB phosphorylation levels as well as by alterations of Arc, COX-2 and NOS1 mRNA expression.

Further investigation revealed that chronic administration of L-lactate induced antidepressant-like effects in two animal models of depression, including the open-space forced swim test and the corticosterone model of depression. In particular, we found that chronic administration of L-lactate partially restored mobility in the open-space forced swim test and completely reversed the corticosterone-induced anhedonia-like behavior. The antidepressant-like effects induced by chronic L-lactate administration were accompanied by changes in the expression of target proteins implicated in serotonin receptor trafficking (p11), astrocyte functions (S100β), neurogenesis (Hes5), nitric oxide synthesis (NOS1) and cAMP signaling (PDE4D).

Collectively, these studies identify a previously unrecognized action of L-lactate by which acute and chronic peripheral administration of L-lactate produces antidepressant-like behavioral responses. Further elucidation of the mechanisms underlying the antidepressant effects of L-lactate may help to identify novel therapeutic targets for the treatment of depression.
Newly designed ecological task to assess cognitive map reading ability:
Behavioral and neuro-anatomic correlates of mental navigation and spatial memory

Faulmann I.

UNIGE - FAPSE

In the frame defined by O'Keefe and Nadel (1978), the so-called cognitive map is thought to be an allocentric – i.e., view-point independent – representation of our environment, built progressively during exploration. Furthermore, the hippocampal place cells (Ekstrom et al., 2003; O'Keefe & Nadel, 1978) are potentially the actual neural substrate of the cognitive map. Aiming toward a better understanding of the CMRT neuroanatomical correlates in humans, and more generally toward a better understanding of how the brain processes the cognitive map, we adapted the CMRT as an fMRI procedure. 23 healthy subjects (11 women, 12 men, 1 left-handed, 22 right-handed, 21-61 aged; M = 29.04, ET = 8.94), all living in Geneva for at least 2 years, underwent the CMRT in fMRI. Results show, for distance and direction taken together, than the most active brain regions are the parietal, frontal and cerebellar parts. Additionally, as expected, patterns of brain activation differ when comparing the two modalities. Furthermore, distance processing seems to rely more on the parietal (compared to other brain regions and to direction processing). It is interesting to notice that no significant activity has been observed in the hippocampus whatsoever.
Resting microstate and heart rate variability does not return to baseline one hour after a submaximal cycling exercise

Spring J.¹, Bourdillon N.¹, Barral J.¹

UNIL, ISSUL¹

Acute physical exercise is known to modulate EEG resting microstate temporal features, especially the map C duration and relative time coverage. Microstate C has been related with the salience resting state network, which is mainly structured around the insula and cingulate, two brain nodes that receive autonomic afferents. Based on the interaction between the brain and the cardiovascular system, this study aims to describe microstate and cardiovascular autonomic activity recovery after a single-bout of physical exercise.

Thirty-eight young adults performed a 25-minutes constant-load cycling exercise at an intensity subjectively perceived as “hard”. Microstate temporal features and conventional time and frequency domain heart rate variability (HRV) were obtained during 5 minutes at rest before exercise (BSL), as well as 5 (P05), 15 (P15), 30 (P30), 45 (P45), and 60 (P60) minutes after exercise cessation.

Compared to BSL, HRV parameters were changed at all post-exercise time points, except the LF/HF ratio in P45 and P60. A main time effect was observed for microstate C duration and time coverage. Post-hoc tests indicated that microstate C duration were significantly different from BSL during the whole post-exercise recovery period.

The present study confirmed that exercise modulates preferentially microstate C duration with an effect extending during the following hour after exercise cessation. Similar long-term effects were found for most HRV parameters, suggesting that microstate changes induced by exercise persist as long as the cardiovascular system does no return to homeostasis. Investigating more precisely the functional interaction between microstate C and HRV would be a relevant perspective.
**Striatum plays a role in the internal generation of temporal regularity: Evidence from a finger tapping task**

Sameiro Barbosa C.¹, Clarke S.¹, Geiser E. ¹

CHUV¹

The perception of temporal structure of auditory stimuli is essential enabling a person to correctly perceive and interact with the environment. Both purely sensory and sensorimotor processing crucially rely on timing perception. The processing of temporal regularity in a stream of sounds is associated with neural activity in the striatum (Geiser et al., 2012). Yet, the specific role that the striatum plays in the processing of temporal regularity remains unclear. The striatum could internally perpetuate temporal regularity (Schiffer & Schubotz, 2011), including the generation of a temporal prediction, or it could confirm internally generated temporal predictions (Grahn & Rowe, 2012). Thus, to disentangle these two potential functions of the striatum in temporal processing, participants performed a sensorimotor synchronization-continuation task in fMRI. Participants were presented with a regular sequence of sounds and asked to tap with their right-hand index in the same tempo as the previously heard sequence while the sequence was repeated (Synchronization) or while a temporally unstructured sound was played (Continuation). Three different tempi were randomly presented in the regular sequence: 195, 293 and 390 ms. For Continuation compared to Synchronization greater activation was found in the caudate across all presented tempi and in the putamen in some tempi. Our results confirm that both the caudate and the putamen play a role in structuring movement in time and, consequently, are associated with the internal generation of temporal regularity.
Fine structure of posterior alpha rhythm in human EEG: Frequency components and their cortical sources

Barzegaran E.

CHUV

Heterogeneity of the posterior alpha rhythm (AR) is a widely assumed but rarely tested phenomenon. We decomposed the posterior AR in the cortical source space with a 3-way PARAFAC technique, taking into account the spatial, frequency, and temporal aspects of high-density EEG. We found a multicomponent AR structure in 73% of a group of 60 healthy adults. The typical resting-state structure consisted of a high-frequency occipito-parietal component of the AR (ARC1) and a low-frequency occipito-temporal component (ARC2), characterized by individual dynamics in time. In a few cases, we found a 3-component structure, with two ARC1s and one ARC2. The AR structures were stable in their frequency and spatial features over weeks to months, thus representing individual EEG alpha phenotypes. Cortical topography, individual stability, and similarity to the primate AR organization link ARC1 to the dorsal visual stream and ARC2 to the ventral one. We have shown that aging affects separately the two components with bigger impact on ARC1. Understanding how many and what kind of posterior AR components contribute to the EEG is essential for clinical neuroscience as an objective basis for AR segmentation and for interpreting AR dynamics under various conditions, both normal and pathological, which can selectively affect individual components.
Copy number variants at the 16p11.2 and 1q21.1 locus are associated with autism, schizophrenia and other neurodevelopment disorders, with significant variance in the severity of specific traits. Although the two CNVs share similar clinical phenotype, the distribution of various phenotypic traits between duplication and deletion carriers follows an opposite pattern. 16p11.2 deletions have been associated with macrocephaly and ASD, and the duplications - with microcephaly and schizophrenia. Conversely in 1q21.1 deletions we observe microcephaly and schizophrenia, in duplications - macrocephaly and ASD. The aim of this study was to investigate the gene-dosage effect on brain anatomy in CNV carriers by investigating shared and differential contribution between deletion and duplications and their interaction in the two CNVs. We demonstrate that both CNVs’ deletions, compared to duplications, are characterized by grey matter volumes increase in the anterior insula, hippocampus, Heschl’s gyri, cerebellar vermis and thalamus, additional to grey matter volumes decrease in the middle frontal gyrus, medial segment of the superior frontal gyrus and middle temporal gyrus. We also observe unique contributions of the two CNVs reflecting the opposite pattern of phenotype traits. Overall this study highlights the importance of comparing and combining data relative to different CNVs that share similar phenotypes in order to increase our understanding of genetic risk factors.
Repetition suppression effect for emotional content

Grisendi T.¹, Reynaud O.², Da Costa S.², Clarke S. ¹

EPFL², CHUV¹

Emotional sounds processing involves interactions between the auditory cortex (AC) and the amygdala (Amy) (Fecteau et al., 2007; Frühholz et al., 2016). Repetition suppression (RS) effect has been observed for non-emotional environmental sounds within the early-stage auditory areas (Da Costa et al., 2015). In this study, we investigate the representation of emotional sounds within early-stage auditory areas, the voice area (VA) (Belin et al., 2000) and Amy, using a RS paradigm.

Subjects listen to a battery of emotional sounds (Aeschlimann et al., 2008) comprising two categories (human vocalizations and non-vocalizations) and three valences (positive, neutral and negative), resulting in six conditions. Classic GLM analysis revealed a strong effect for the contrast ‘Sounds vs. Silence’ on the supratemporal plane, STG and STS (q(FDR)<0.05, p<0.002). The contrast ‘Human vocalizations vs. Non-vocalizations’ highlighted a strong activation in STS, in the region corresponding to VA (q(FDR)<0.05, p<0.0004). Finally the contrast ‘Emotional sounds vs. Neutral sounds’ resulted in restricted activations in STG (q(FDR)<0.05, p<0.0001), and Amy (p<0.009, uncorrected). BOLD time-courses revealed a clear preference of VA for human vocalizations. This preference was also present, to a lesser extent, in the AC. Amy preferred emotional sounds compared to neutral sounds, while AC and VA showed the reverse. We observed a general effect of RS in each region, with a stronger effect for human vocalizations in VA and emotional sounds in Amy.

Overall, our results showed a strong repetition suppression effect for the affective information of vocal and environmental sounds in both auditory areas and amygdalae.
Using wavelet correlations to examine the impact of smells on resting state

Carlson H.

UNIGE - CMU

Emotional experiences are likely to influence how we process information, but a growing number of studies have suggested that small, transient emotions can influence subsequent mental activity. Increasingly, resting state is being used by investigators as a way to study the impact of emotions on the brain. To study this, we investigated how positive and negative smells differentially influenced transient emotions during the subsequent brain activity at rest. We acquired fMRI data in 20 participants during rest periods following positive and negative smells. The experiment was divided in to 2 session on two different days, one for pleasant smells (positive emotions) and one for unpleasant smells (negative emotions). Functional connectivity at different frequency bands was assessed using a wavelet correlation approach and small-world analysis.
Learning statistical regularities in 8 to 12 years old is associated to sustained attention and video-game use.

Buchard A.\textsuperscript{1}, Schrater P.\textsuperscript{2}, Cardoso-Leite P.\textsuperscript{1}, Bavelier D. \textsuperscript{1}

UNIGE - FAPSE\textsuperscript{1}, Departments of Psychology and 2 Computer Science, University of Minnesota\textsuperscript{2}

This study presents a new visuospatial task designed to measure ‘structural learning’ or the faculty to uncover statistical regularities common to several tasks through experience. Attentional control skills (Conners, SDQ, D2, SART, Lachaux attention tasks), as well as academic performance, wellbeing, lifestyle, and video-game play habits were also evaluated to inquire about the maturation and determinants of such learning in children. Children [N=95] played “Catch-the-Wolf”, a visuospatial learning game in which participants have to infer the trajectory followed by a wolf in order to catch it. Children played this game four times with four different wolves. A key aspect is that the behavior of these different wolves, although locally different, is governed by a common generative model. Thus, learning the behavior of Wolf 4 will be facilitated for participants best able to infer the common generative model from their experience with preceding wolves. As expected, accuracy and processing speed on the attention and learning tasks improved with age. A PCA summarized individual differences, and three main independent components predicted accuracy: a) being faster and older, b) having better-sustained attention, and c) greater use of video games in boys. Only the first component predicted the speed of execution of the learning task.

This study presents a new, short (20min) entirely computer-administered task through which the ability to create and update internal models through experience can be measured. Variance related to sustained attention and video-game usage was found to relate to such learning skills.
Targeting Redox dysregulation in schizophrenia: Synthesis and testing of novel cysteine analogs

Skupienski R.

CNP/CHUV

The present treatments against schizophrenia reduce suffering, but they are mainly symptomatic, partly inefficient, and have major side effects. There is the need to find new therapeutic approaches. Administration of the glutathione (GSH) precursor N-acetylcysteine (NAC) to chronic patients, leaded to an improvement in symptoms not well treated with antipsychotics. NAC however has several major drawbacks. It does not cross well the blood-brain barrier and it shows a limited efficiency.

The aim of the project is to synthesize and test novel precursors and analogues of GSH. We design new cysteine analogs to be more lipophilic and hydrophobic than NAC. In parallel, we are developing a method to assess the redox homeostasis in mouse brain by 31P MRS which permits the quantification of the NAD+/NADH ratio. This ratio, which is reported to be altered in patients, is a good indicator of tissue redox balance and bioenergy. As first in vivo model, mice are treated with phencyclidine (PCP) which impairs the prepulse inhibition (PPI). A PPI deficit indicates anomalies in sensorimotor gating which is also affected in patients.

We synthesized 22 new compounds which exhibit antioxidant properties and better bioavailability than NAC (in silico). A new coil 1H-31P for 14.1 Tesla Magnet has been manufactured and is currently used to validate the technique in mice cortex at different developmental time points. A pretreatment with one of the lead compound partially reverses the PPI deficit induced by PCP in a dose-dependent manner. We are currently comparing the efficacy of this compound with that of NAC.
Constitutional differences in corticosterone adaptation to stress are related to fear conditioning in rats.

Monari S.¹, Walker S.¹, Huzard D.¹, Guillot de Suduiraut I.¹, Zanoletti O.¹, Astori S. ¹

EPFL - BMI¹

The hypothalamus-pituitary-adrenal (HPA) axis represents a major stress-activated system that enables an individual to cope with stressful adversities. The activity of the HPA axis is regulated by multiple afferents, and its activation leads to the final release of glucocorticoids. Dysfunction of the HPA axis activity is thought to play an important role in stress-related psychopathologies, such as post-traumatic stress disorder (PTSD). Studies on humans have shown that individual differences exist in the vulnerability of developing PTSD during the course of life. However, whether individual differences in stress habituation are causally implicated in vulnerability to anxiety-related disorders is not yet clear. To address this question, starting from a population of Wistar outbred rats, we generated lines of animals selected for their differential ability to habituate to stress, as measured by glucocorticoid responsiveness to a stress reactivity test at postnatal day 30. In this study, we characterized cued fear acquisition, extinction and remote memory in rats selected as high, intermediate and low responders. We found that both high and low rat lines displayed deficits in fear extinction, with increased freezing response to the conditioned stimulus as compared to intermediate lines. Interestingly, low line rats also retained elevated freezing at remote testing, thus exhibiting a persistent fear memory indicative of PTSD. We are currently performing EEG analyses to investigate whether individual differences in corticosterone response to stress are related to sleep alterations. Taken together, our findings suggest that constitutive differences in stress habituation are associated with vulnerability to develop anxiety disorders.
Why do Montessori Fosters Creative Thinking? Children Learn to Act Slow and Self-Regulate Mistakes

Denervaud S.¹, Gentaz E. ²

UNIGE - CISA¹, UNIGE- FAPSE²

We aimed at studying interactions between academic outcomes, executive functions, emotional well-being at school, creativity, selective attention and post-error self-regulation, in different learning environments (Montessori and traditional) to assess early key factors of success. Ninety children underwent a complete assessment, with a pair-matched design. Here we show that Montessori participants systematically achieved significantly higher scores in academic and creativity tasks, reproducing existing data (Lillard & Else Quest, 2006, Besancon & Lubart, 2007). More originally, results unveil that even if executive functions are strongly impacting academic outcomes (Diamond, 2011), it is creativity that is the main significant predictor. Furthermore, creative thinking was found to take place in case of slowed attention processes combined with post-error self-regulation. These findings are a first step towards understanding how creative thinking, which seems to results from both creativity and knowledge combined, can take place, with self-regulation strategies as a part of it, such as one’s own emotional relationship to mistakes and enabling time to think. These self-regulation strategies were shown to be shaped differently according to the learning environments. This sheds light on the importance of setting adequate school environments from early years on.
EEG recording during an emotional face matching task in children of mothers with interpersonal violence-related posttraumatic stress disorder

Perizzolo V.¹, Berchio C.², Puro Gomez C.³, Vital M.⁴, Arnautovic E.⁴, Carpinteiro V.⁴, Schneeberger M.³, Manini A.³, Torrisi R.³, Rusconi Serpa S.³, Schechter D.³

HUG⁴, UNIGE - HUG¹, UNIGE², UNIGE-HUG³

The Geneva Early Childhood Stress Project is a longitudinal research considering mothers exposed to interpersonal violence-related posttraumatic stress disorders (IPV-PTSD), non-PTSD controls, and their children. A goal of the follow-up of this study aims to find differences in emotional processing between children of these two groups of mothers. High density EEG was recorded during an Emotional Face Matching Task (EFMT). Given the results obtained in Phase 1 of the project, in which disturbances in emotion and arousal regulation were found to distinguish IPV-PTSD mothers and their children as compared to the controls and their children at ages 12-42 months, we expect to find that, in Phase 2 of the study, children of IPV-PTSD mothers will present greater difficulty in identifying emotional faces compared to controls. We also expect a difference in the amplitude of event-related potentials (ERPs) that are involved in the perception and processing of facial expressions and associated emotions.

Preliminary results showed a trend for a decreased number of correct answers and an increased RT for all emotions during the EFMT among children of IPV-PTSD mothers when compared to those of controls. In addition, HD-EEG recorded in response to specific emotions supported the idea of differences in facial processing, given the higher amplitude observed in ERP component N170 among the control group. Our preliminary results seem to provide evidences that IPV and related maternal PTSD likely influence child emotion-appraisal and may have an attentional bias in processing emotional faces.
Playing for a virtual audience: Expressive features in musical performances

Schaerlaeken S.¹, Glowinski D.², Grandjean D. ³

UNIGE - Faculté des Sciences¹, UNIGE - CISA², UNIGE - FAPSE³

Immersive Virtual Environments combined with motion capture systems have been used as experimental set-ups for studying musicians’ performances in different contexts. By exploring both acoustic and motion features, this study highlights the impact of the presence of a virtual audience on both the performance and the perception of authenticity and emotional intensity by the listeners. Gestures and sounds produced were impacted differently when musicians were asked to play with different expressive intents. The presence of an audience reduced the differences between those categories and makes them converging towards values associated with the projected expressive manner. On the listeners’ side, only the congruent situation of projected expressive intent and the presence of an audience boosted the participants’ ratings in both authenticity and emotional intensity. When comparing the different features values, stimuli recorded with an audience were associated with a bipartite distribution of the values for both authenticity and emotional intensity (either high or low) contradicting the three artificially created expressive categories. This study highlights the use of IVEs as a research tool as well as a training assistant for musician eager to learn how to cope with audience anxiety.
Abnormal electrophysiological correlates in patients with left medio-temporal lesion.

Tautvydaite D.¹, Manuel A.¹, Schnider A.¹

UNIGE - HUG¹

Immediately repeated stimuli are less well recognized after a delay than stimuli repeated after intervening items, an effect known as the Spacing effect. However, we have previously found that stimuli repeated immediately within a continuous recognition task evoke a frontal potential at 200-300 ms, which emanates from the (left) medial temporal lobe (MTL) and has a protective effect on the memory trace. Patients with Wernicke-Korsakoff syndrome were shown to lack this frontal potential. Here, we tested 11 patients with focal left medial temporal lesions and amnesia, compared to healthy controls, to verify whether this frontal potential would also be absent in patients. Brain activity was measured with high-density EEG as subjects made a continuous recognition task containing both immediately repeated stimuli and stimuli repeated after 9 intervening items. Both patients and controls had a spacing effect: after 30 minutes, they recognized new presentations and pictures repeated after intervening items better than immediate repetitions. Patients’ performance was significantly poorer than controls during encoding and delayed recognition tasks. Importantly, only controls, but not the patients, expressed the frontal positive potential at 200-300 ms in response to immediate item repetition. The observations further support the utility of immediate picture repetition for testing the integrity of MTL functioning. Also, they support the idea that this early frontal potential (emanating from the MTL) has a memory-protective effect.
Major depressive disorder (MDD) is the second main cause of disability in the world. Electroconvulsive therapy (ECT) is an effective therapeutic for treatment resistant depression (TRD) with a remission rate of 80%. Although commonly used, the precise mechanisms of impact on mood and behaviour remain elusive. The present study investigates the neuroplastic effects induced by ECT in patients with TRD and links this to individual's trajectory of behavioural changes. We combine structural quantitative (qMRI) and functional magnetic resonance imaging with a pattern separation (PS) task to test the hypothesis that the behavioural changes in due course of ECT are causally linked to structural and functional brain plasticity. The experimental group (N=3) is tested before ECT treatment (t0), after one session (t1), at the end of the treatment (t2) and 6 months later (t3). A control group of MDD patients not receiving ECT (N=2) undergoes the same protocol.

Our preliminary analysis given the current sample size allows only for descriptive inference with limited statistical power. We observed a trend for hippocampal volume increase at t2 that was not present in the control group. PS performance decreased at t2 in the experimental group, whereas it slightly increases in the control group. Our findings are in line with the existing literature on hippocampus volume changes after ECT, whilst extending current knowledge by providing the opportunity for a more straightforward neurobiological interpretation by using qMRI and to combine anatomical, functional and behavioural into a single model.
Experimental analysis of Hyper Anxiety in Mild Cognitive Impairment

Blake Y.\(^1\), Terburg D.\(^2\), Von Gunten A.\(^3\), van Honk J.\(^4\), Stoop R. \(^1\)

University of Utrecht\(^2\), SUPAA/CHUV\(^3\), University of Cape Town\(^4\), CNP/CHUV\(^1\)

This project aims to examine hyper-anxiety in patients with Mild Cognitive Impairment (MCI). Emotional symptoms, including anxiety, are frequently observed in MCI and Alzheimer’s disease (AD) patients and present a major difficulty for both patients and caregivers.

This project focuses on the role of the basolateral and central amygdala (BLA and CeA) in these symptoms, as these are critical brain region for anxiety behaviours, and amygdala atrophy is a common early neurological symptom of MCI and AD. The CeA is important for the unconditioned, instinctive fear response, whereas the BLA is more cortical and can exert modulatory control over CeA function. Recent evidence suggest that the amygdala damage in MCI and AD patients is limited to the BLA, while the CeA remains intact.

Recently it has been shown that patients with bilateral, circumscribed BLA lesions show hyper-anxiety, likely arising from a loss of inhibitory control of the BLA over the CeA. Hyper-anxiety in MCI patients may similarly be related to a loss of inhibitory control of the BLA over the CeA.

In an attempt to test the ability to inhibit anxiety I run a threat and escape task (TAET) which manipulates the proximity of a threat in order to differentially activate OFC-BLA pathways (by distal threat) and the CeA-brainstem pathway (by proximal threat). In addition, I am using an episodic memory task to investigate the effect of emotion on episodic memory in the UWD and MCI patient groups. Here I show preliminary results for these tasks.
A cross-species study of the impact of auditory memory reactivation during sleep on generalization learning in humans and rats

Klaassen A.-L.¹, Rasch B.¹, Rainer G. ¹

University of Fribourg¹

Studies in humans have shown a beneficial impact of sleep on generalization learning. To explain these effects, the “information overlap to abstract” hypothesis suggests that new schemata are formed during slow wave sleep due to overlap in reactivated memories. To test this hypothesis, for sleep dependent auditory generalization learning, we developed a cross-species approach using similar experiments of auditory learning in humans and rats. Here, during the initial learning task, humans and rats learned to associate auditory stimuli with reward-related behavioral responses. Subsequently, during slow wave sleep, selected previous learned stimuli were re-presented to test the effect of target auditory memory reactivation on generalization performance after sleep. Based on preliminary data, we observed that memory and generalization performances of the sleep-reactivated stimuli were enhanced in comparison to the non-reactivated stimuli. By conducting this cross-species experimental approach, we aim to investigate the neuronal correlates of auditory memory reactivation on different levels by combining the human EEG with intracranial electrophysiology in the rat model.
Behavioral investigation of visual selective attention mechanisms in humans

Pagnotta M.¹, Plomp G. ¹

University of Fribourg¹

Mechanisms of visual selective attention prioritize behaviorally relevant over irrelevant stimuli to increase information processing efficiency. Task-relevant information may be selected on the basis of low-level features (feature-based attention, FBA) or more complex representations (object-based attention, OBA). We tested a new paradigm to investigate FBA and OBA under changing task demands, with the ultimate goal of using this paradigm to better understand the neural processes involved.

Stimuli consisted of random-dot kinematograms (RDK) and oriented Gabor gratings (GG) presented under different conditions: 1) superimposed RDK and GG (combined-objects); 2) RDK with grey-scale values defined by GG (combined-features); 3) RDK or GG individually (control). Each stimulus condition was presented in two task conditions (orientation discrimination, motion discrimination). We measured discrimination thresholds in each task by varying either motion coherence of the RDKs, or angle of the GGs, using an adaptive staircase algorithm.

Twenty-nine subjects performed the attentional tasks. Subjects were able to perform the two tasks on different stimuli. We observed increases in both thresholds for combined-objects and combined-features stimuli compared to control. Results revealed statistically significant distracting effects of the irrelevant feature in orientation-discrimination task, with increased threshold for combined-objects relative to control, and for combined-features relative to combined-objects, suggesting that motion is processed even when it is task-irrelevant, and especially when the two features are bounded. In a follow-up study, we acquired EEG and fMRI data in twenty other subjects while performing the tasks under combined-objects and combined-features conditions. Preliminary behavioral results confirmed the effects observed in the pilot.
Keeping track of sound objects in space.

Da Costa S.\textsuperscript{1}, Gruetter R.\textsuperscript{1}, Crottaz-Herbette S.\textsuperscript{2}, Clarke S. \textsuperscript{2}

EPFL - CIBM\textsuperscript{1}, CHUV - NPR\textsuperscript{2}

The dual-stream model stipulates that sound localization takes part in the dorsal stream. However, Bourquin et al. (2013) proposed a new model with a third stream where position-linked representations of sound objects are distinct from the sound meaning and explicit sound localization. Here we investigated how early auditory areas integrate sound object meaning and binaural cues using a repetition suppression (RS) fMRI paradigm at 7T. Subjects listen passively to environmental sounds presented in 30s-blocks of eight repetitions of the same sound object category or eight different sounds objects categories. These sounds were either in the centre, left or right or shifted left-to-right or right-to-left after 8s (change within block). Time-courses were extract with BrainVoyager, and then statistically analysed using MATLAB scripts. GLM contrast Sound > Silence revealed activations in bilateral STG, right MTG and right IFG. An ANOVA 2 (Category) x 2 (Change) x 2 (Hemisphere) on the BOLD responses showed: main effect of Category in primary auditory cortex (PAC) and planum temporale; main effect of Change in PAC; main effect of Hemisphere in posterior lateral Heschl’s gyrus (latHG); interaction Category X Hemisphere in PAC; interaction Category X Change in latHG, interaction Category X Change X Hemisphere in latHG. BOLD responses showed a greater response for contralateral hemispace and clear RS effect for both Category and Change in latHG. Overall, our results showed repetition suppression for Category and Change in posterior lateral HG in agreement with the model of a position-linked representation of sound objects at the early stage level.
Temporal Gestalt perception: Where in the human brain do we encode rhythm?

Notter M.¹, Hanke M.², Murray M.³, Geiser E. ⁴

CHUV - LINE/CIBM/HOJG; VU - Hearing and Speech Sciences³, CHUV - LINE/NPR; MIT - McGovern Institute⁴, OVGU - Psychoinformatics lab², CHUV - LINE/CIBM¹

Hearing is the perception of a temporal structure over time. This structure is created by the relative temporal proximity between acoustic events and leads to the percept of a temporal Gestalt. So far, brain mechanisms underlying the perception of temporal Gestalt are unknown. We conducted a functional Magnetic Resonance Imaging (fMRI) study, in which participants listened to short sound sequences of three different rhythmic Gestalts. All rhythms were presented in three different tempi and with two different instruments. We trained a linear support vector machine (SVM) classifier to differentiate the activation pattern of the three temporal Gestalt. By using different tempi and different instruments we force the classifier to generalize over those properties and decode the perceived rhythmic Gestalt. A searchlight analysis showed that the temporal structure of the rhythms is encoded bilaterally by the activation pattern in the temporo-parietal junction (TPJ), including the planum temporale, and unilaterally in the right inferior frontal gyrus. These results expand the already confirmed role of supramodal areas of the TPJ in Gestalt processing, to the perception of auditory temporal Gestalt. We show for the first time that sensory areas not only process absolute temporal intervals of sounds, but also integrate them into the percept of a rhythmic Gestalt and that the encoding of these percepts persists in high-level associative areas.
Effect of acute physical exercise on procedural memory

Marin Bosch B.¹, Bringard A.², Logrieco M.¹, Immobersteg N.¹, Thomas A.³, Ferretti G.¹, Schwartz S.¹, Igloi K. ¹

CURML³, UNIGE ¹, UNIGE²

Strong evidence suggests that regular physical exercise improves cognitive functions, especially in the memory domain by increasing neurogenesis in the hippocampus. The effects of acute physical exercise on cognition are less well understood. In animals, a single session of physical exercise has been shown to boost BDNF (Brain Derived Neurotrophic Factor) levels, a growth factor known to enhance neurogenesis and plasticity in the hippocampus.

In this study we combined blood biomarkers, behavioral measures and fMRI to assess the impact of medium and high intensity acute physical exercise on procedural memory and underlying biomechanisms in humans. For this, we tested procedural memory in twenty healthy participants across three visits using a serial reaction time task (SRTT) performed in fMRI before and after a period of exercise (moderate or high intensity) or rest. Additionally, participants wore a near infrared spectroscopy (NIRS) probe over the prefrontal cortex during exercise and rest and blood samples were taken before and after exercise and rest.

We report an overarching effect of physical exercise: increasing performance levels (p=0.013), enhancing BDNF (p=0.045) and NIRS signalin (p=0.002). Further, we also found selective activation of the bilateral putamen during SRTT after moderate intensity exercise vs SRTT after rest. Links between performance, BDNF, NIRS and fMRI measures are being further explored. Overall, these findings shed light on the biomechanisms underlying the beneficial influence of acute physical exercise on human cognitive functions.
The Influence of Transient Affective states on attention tasks

Gaviria J.\textsuperscript{1}, Vuilleumier P.\textsuperscript{2}, Van de Ville D.\textsuperscript{3}

UNIGE-EPFL\textsuperscript{3}, UNIGE - FAPSE\textsuperscript{1}, UNIGE-Medicine\textsuperscript{2}

Conflict adaptation has been widely researched in normal and clinical populations. No study to date has examined how the temporal dynamics of the intrinsic functional networks is related to behavioral conflict adaptation, and how it is modulated by different emotional events. The functional connectivity dynamics (FCD) of the Resting-state functional magnetic resonance imaging (RS-fMRI) is a promising tool to investigate this issue. The present study evaluated both the functional connectivity (FC) and the co-activation patterns (CAPs’) of the RS-fMRI signals in order to explore the neural basis of the emotional modulation of conflict adaptation across 28 healthy subjects. GLM and PPI analysis were carried out to identify regions of interest (ROIs) playing a key role on the relationship between the changes in BOLD response and behavioral conflict adaptation as a function of negative-valence transient emotional events. The results show that CAPs’ maps from bilateral superior parietal lobule and the dorsal anterior cingulate cortex (dACC), are spatially overlapping and their sustained-activity signals temporally overlap with CAPS form the left anterior insula and right inferior frontal gyrus. This space-temporal overlap between CAPs is consistent with behavioral features of the emotional modulation of the conflict adaptation.
Identifying distinct learning strategies in humans during a complex task

Lehmann M.¹, Liakoni V.¹, Gerstner W.¹, Preuschhoff K. ²

Geneva Finance Research Institute², EPFL - BMI¹

Recent advances in computational, behavioral and cognitive neuroscience have indicated that humans employ multiple reinforcement learning (RL) strategies to learn from the outcome of their actions. Nonetheless, our understanding of learning behavior is still largely restricted. Here we employ a novel multi-step sequential decision making task alongside a larger repertoire of algorithms to explain human learning behavior. To facilitate fMRI data analysis, the experiment is designed to de-correlate signals of different strategies. Twenty-three human subjects performed the task in an fMRI scanner. We considered the following algorithms: three model-free (MF) value-based algorithms, one model-based (MB) algorithm, an MF-MB hybrid learner and a policy gradient algorithm. We find correlates of MF prediction errors in the ventral striatum and other areas and MB correlates in the inferior frontal gyrus and insula. Our results support the existence of two systems in the brain performing MF and MB computations, in agreement with previous studies. Importantly, our behavioral data are best explained by a policy gradient algorithm and by an update of actions based on eligibility traces and end-of-episode reward, rather than intermediate errors. Our study introduces a new more complex task, designed to mitigate the correlation of MF and MB signals. We extend previous findings in this multi-step scenario and test whether algorithms other than the ones usually considered in RL human studies are a closer description of behavior. Our results bring forward a policy gradient algorithm, that may have implications in our regard on human learning.
Immediate and Long-lasting Effects of Cortisol Suppression on the Retrieval of Emotional Memories in Humans

Antypa D.¹, Vuilleumier P.², Rimmele U.²

UNIGE - Other¹, UNIGE²

Emotional memories are formed to last: concerted action by key stress-related neuromodulators promotes memory encoding and consolidation within a complex brain network (Roozendaal et al., 2009; McGaugh, 2000). Maladaptive retrieval of emotional memories is thought to underlie stress-related disorders (e.g. post-traumatic stress disorder), and thus retrieval has been proposed as potential target for their treatment (de Quervain et al., 2017; Buchanan, 2007). Cortisol suppression has been shown to weaken both immediate and long-term retrieval of emotional memories (Rimmele et al., 2015; Marin et al., 2011), however the underlying neural mechanisms have not yet been documented.

Using fMRI, we investigated brain activity associated with cued recall of previously learned word-scene associations of emotional and neutral stimuli during the morning rise of cortisol and during manipulated cortisol suppression. Formed memories were again tested four days after cortisol manipulation in order to examine long-term effects on memory performance. In line with previous research, we found that cortisol suppression weakened immediate and long-term retrieval of emotional memories. Preliminary analyses of the fMRI data showed that cued recall of emotional scenes (vs. neutral scenes), during the physiological rise of cortisol, was associated with increased activation in the ventromedial prefrontal cortex, right parahippocampal cortex and bilateral amygdalae. However, during cortisol suppression, there were no observed differences in BOLD activation for the recall of emotional vs. neutral scenes. Taken together, these results support the idea that retrieval of emotional material during cortisol suppression may change the representations of emotional memories in the human brain.
Sex differences in visuospatial transformation: effects on event-related potentials N100, N200

Nguyen N.

UNIL - DP

Tasks involving manipulations and transformations of visuospatial images revealed a consistent men advantage over women. A recursive factor to explain the differences between sexes is that they are the result of differences in the strategies used to process information. However, strategies have been mainly assessed through event-related potentials (ERP) recorded at the late stage of information processing and mostly during object-based transformations as in classical mental rotation tasks. Here, we investigate ERPs at the early stage of visual processing in both observer-based and object-based visuospatial transformations in order to better understand the nature of this difference. Fifty participants (21 females and 29 males) were trained in a classical 3D mental rotation (object-based condition) and a perspective-taking (observer-based condition) tasks. Averaged peak amplitudes of negative components N100 and N200 were examined to assess attentive processes. Preliminary results reveal that men made less error than women in both tasks, although reaction times were similar. Regarding ERP, they showed: i) significant differences between amplitude for each type of visuo-spatial transformation in parietal-occipital, regions known to be involved in visuo-spatial transformations; ii) an increase in both N100 and N200 amplitudes in women by comparison with men whatever the task was. Taken together, these results suggest that women and men do not process perspective taking and mental rotation tasks in the same way. By comparison with men, women exhibit greater cortical involvement already at the early stage of visual processing. Sex main effects might indicate a possible higher requirement of cognitive resources in mental rotation and in perspective taking, but exclusively in women and this difference might rely on a more efficient processing of visual informations in men.
Exploring the Effects of Chronic Cocaine Self-Administration on Behavior and on Striatal D2/3 Receptors Density in the Roman High- and Low-avoidance Rats

Dimiziani A.¹, Belles L.¹, Tournier B.², Tsartsalis S.³, Millet P.³, Ginovart N.³

HUG, UNIGE - Belle-Idée³, UNIGE - Belle-Idée¹, HUG²

Cocaine abuse has been linked to novelty seeking (NS) and impulsivity personality traits. In this context, D2/3 receptors have been shown to play a critical role. However, the causal relations, as well as reciprocal influences, linking such factors remain unclear. The aim of our study is to test behavioral traits and striatal D2/3 receptors density in a rat model displaying different phenotypes and observe changes following chronic cocaine self-administration. We use the Roman High- (RHA) and Low- (RLA) avoidance rats’ lines that display innate differences in impulsivity and novelty seeking, with the former being more novelty seeker and impulsive than the latter, as well as marked differences in cocaine self-administration, with RHAs being more vulnerable to the drug. Moreover, RHAs have been shown to have a lower striatal D2/3 receptors density when compared to RLAs. After measuring NS with the novelty-induced place preference task, and impulsivity with the 5-choices serial reaction time test, D2/3 receptors density is quantified through a SPECT scanner using the D2/3 antagonist radioligand [123I]IBZM. Then, rats are trained to self-administer cocaine (0.4 mg/kg/infusion) for 15 days. Finally, NS and impulsivity are tested again, after which a second SPECT scan follows in order to observe changes in D2/3 receptors density.
Probing action video games impact on the processing of attended and unattended emotional stimuli using SSVEP and ERP

Ciobanu A.¹, Andersen S.², Bediou B.¹, Föcker J.³, Bavelier D. ⁴

University of Aberdeen², UNIGE - FAPSE¹, University of Geneva and University of Rochester⁴, Ludwig-Maximilians-Universität München³

In the present study we investigated whether enhanced attentional control previously documented in action video game players for non-emotional stimuli also extends to emotional stimuli. Young adults with high (AVGPs) or no action video game experience (NVGPs) were compared on several behavioral and electrophysiological measures acquired during a facial emotions detection task. Both groups showed similar performance in terms of accuracy and reaction time, as well as comparable SSVEP to attended and unattended streams of emotional faces. Some weak signs of worse performance in AVGPs were suggested by their larger RT variability when detecting targets in the right visual field. ERP analyses revealed a stronger early neural response to targets in AVGPs relative to NVGPs as indicated by P1 amplitude, consistent with the previously documented increased contrast sensitivity in AVGPs. However, there were no significant group differences on later ERP components: N2pc, P3 and ERN. Regardless of video game experience, our study revealed a robust modulation of SSVEP amplitudes by attention, as well as enhanced SSVEP and performance when attending the left as compared to the right stream, in line with the documented right-hemisphere advantage in the processing of faces. In addition, we found that better performance was associated with increased amplitudes of P1 to targets and P3 to hits. Taken together, these results suggest that, when presented with emotional stimuli, AVGPs relative to NVGPs do not exhibit a better attentional control that would be predicted based on studies that used non-emotional stimuli, despite their enhanced early sensory processing.
How does complex versus simple Go/NoGo training improve motor inhibitory control? An electroimaging study

Simonet M.

UNIL-ISSUL

Inhibitory control (IC), a key aspect of executive functions, refers to the ability to suppress cognitive or motor processes. Although several studies have reported increased capacity to inhibit motor responses after short-term training, whether the complexity of training influences the behavioural performance and the cortical changes remains poorly understood. So far, it has been reported that IC can be improved if the top-down control mechanisms are constantly solicited during the training session (see Spierer et al. 2013 for review). Accordingly, one could hypothesize that the practice of a high cognitive load (HCL) task involving an IC component would modify fundamental IC performance and the underlying brain networks.

Using electrical neuroimaging methods, we investigated the effects of 50 minutes IC training in two groups of young adults by comparing the effects of low (n=17) versus high (n=18) cognitive load Go/NoGo training. In the HCL task, switching processes and interference effects were combined with inhibitory processes.

After 50 minutes of HCL training, our results partially corroborate the benefits of the interplay between executive functions on IC performance. Indeed, if RTs are significantly improved after training, the electro-cortical data do not show any modulations within the inhibition network. Instead, the switching processes appear to be quite weighty at the first stage of practice in the HCL group and might hinder (or delay) the improvements of the IC per se. Consequently, we did not observe transfer effects to remote cognitive tasks, even though a near transfer (pure inhibition) is noticeable in the two groups.
Lifespan brain tissue changes reveal a modular architecture of human white matter

Slater D.¹, Melie-Garcia L.¹, Smith R.², Vollenweider P.³, Preisig M.⁴, Kherif F.¹, Lutti A.¹, Draganski B.¹

Department of General Medicine - CHUV³, LREN - CHUV¹, The Florey Institute of Neuroscience and Mental Health, Australia², Department of Psychiatry - CHUV⁴

Understanding the modulation of action, perception and cognition across the lifespan requires in-depth investigation of the processes governing brain tissue changes in human white matter. We use quantitative magnetic resonance imaging (qMRI) biomarkers indicative of tissue myelination and iron levels in combination with diffusion-weighted microstructural imaging and tractography to study age related white matter tissue changes in a large cohort of more than 600 healthy participants. Using a “connectome” approach we discover five unique white matter modules of synchronized lifespan tissue change that overlap spatially with distinct brain function systems and provide quantitative support for two retrogenesis hypotheses of aging. We interpret our findings in the context of modular structural connectivity networks that advance throughout the lifespan according to a hierarchical architecture of maturation and degradation, driving age related changes to cognition and behavior.
Neural correlates of socio-emotional perception in the 22q11.2 deletion syndrome

Dubourg L.¹, Schneider M.¹, Vritcka P.², Debbané M.¹, Chambaz L.¹, , Eliez S. ¹

DIP Lab¹, Max Planck Institutre²

Background: The 22q11.2 deletion syndrome (22q11DS) is a neurogenetic disorder associated with elevated risk for schizophrenia and high rates of distinct positive and negative symptoms. Social impairments were also described in this population, but the neural correlates underlying these impairments are largely unknown. In this study, we investigated neural substrates of socio-emotional experience.

Method: We used event-related functional magnetic resonance imaging (fMRI) to explore neural activity in individuals with 22q11DS and healthy controls during the processing of visual pictorial stimuli varying in social content (social or non-social) or emotional valence (positive or negative).

Results: In the 22q11DS population compared to controls, we found neural hypo-responsiveness in terms of decreased activation in response to social versus non-social images in the inferior parietal lobule, precuneus, posterior cingulate, frontal regions, supramarginal gyrus, superior temporal gyri, and anterior cingulate cortex. Second, we observed a similar pattern of activation for positive and negative emotion processing in the two groups. Finally, we did not observe any social x valence interaction differences between patients and controls.

Conclusions: Our results indicate atypical neural processing of social information in 22q11DS that appear to be independent of concomitant valence processing. Abnormalities in the social perception network may partially explain social impairments observed in 22q11DS individuals.
Emotional regulation revealed by Local Field Potential

Guex R.

UNIGE - CMU

Understanding where, when and how emotional regulation occurs is of crucial importance to cure related mental disease. Recording Local Field Potentials in six epileptic patients, we found in the basolateral Amygdala, the Insula and the Caudate Nucleus, that while free emotional appraisal occurs between ~120ms and ~650ms post stimuli onset, reappraisal and suppression strategy increase electrophysiological activity already around 200ms in a valence specific, in time and space, fashion.
Effects of Atomoxetine and Cognitive remediation on executive functioning in adolescents with ADHD

Ackermann S.¹, Fornari E.¹, Urben S.¹, Halfon O.¹, Bader M.¹

CHUV¹

Objectives:
A meta-analysis in children with Attention Deficit/Hyperactivity Disorder (ADHD) revealed difficulties in executive functions, specifically working memory (WM). In this project, we propose to perform two different studies on 55 adolescents suffering from ADHD and compare them with a group of 37 age, sex and socio-economic status matched controls. Using functional brain imaging (fMRI) and a behavioural task, we will study the effects of Atomoxetine (ATO), Methylphenidate (MPH) and Cognitive Working Memory Training (CWMT) in a prolonged administration (10 weeks). These three interventions have been demonstrated to increase performance in WM in ADHD.

Methods:
Subjects underwent Working Memory-fMRI experiment at two time-points: once before any medication and/or CWMT (T1) and a second time after the drug treatment or after 5 weeks of a cognitive remediation training (T2). A sequence presented during MR scanning will be generated using a PC computer using E-prime software (Psychology Software Tools, Inc), and projected via an LCD projector onto a screen placed in front of the subject’s eyes.

Results/Conclusion:
The fMRI results show that activation start bilaterally high order visual areas extending to parietal regions involved in multisensory integration and visual-spatial processing, in all groups. Maps activation of encoding and retrieval are characteristics of Working Memory pattern. However, if ATO intervention did not show striking effects on WM patterns, the CWMT showed a significant increase of the left inferior frontal sulcus in the retrieval condition and of bilateral insula, angular gyrus and left frontal cortex during the encoding process.
**Brain connectivity in schizophrenia**

Habiby Alaoui S.¹, Guggisberg A.¹, Thézé R.¹, Manuel Stocker A.¹, Schnider A.¹

UNIGE - HUG¹

Orbitofrontal reality filtering (ORFi) denotes a memory control mechanism that allows differentiating thoughts pertaining to the ongoing reality from those that do not. This mechanism has been described in confabulating patients suffering from disorientation and amnesia and relies on intact orbitofrontal cortex and its connections (OFC). Schizophrenia is also characterized by deficits in reality perception and by structural deficits, which include the OFC and medio-temporal lobe (MTL). Here we test whether disturbed connectivity of these regions might also account for reality perception deficits in schizophrenia. Fifteen patients with schizophrenia and 17 age-matched healthy controls underwent Diffusion Tensor Imaging (DTI). Fractional anisotropy and direction map were used to define both diffusion and direction of water molecules. Preliminary results show that schizophrenic patients had a significant impairment in white matter connectivity in the left uncinate fasciculus compared to healthy subjects. These findings suggest a decreased structural connectivity between the OFC and MTL in schizophrenic patients which may underlie reality perception deficits in this population.
**Transient emotional episodes modulate the neural circuits of pain and empathy**

Qiao-Tasserit E.

UNIGE-Medicine

Happiness and well-being are intimately linked to our social environment network and interactions with others. It is then critically important to identify factors that may improve social skills. Here, we tested whether (and how) one’s own emotions could influence empathy and theory of mind when appraising the affective state of others. In a first experiment, we used the model of pain to assess the effect of emotions on empathy. We used positive, neutral, and negative video clips to induce emotions in healthy people. After each movie clip, participants received a painful or painless thermal stimulation (first-hand pain), or watched images of wounded hands (others’ pain). Brain responses to first-hand pain were reduced after positive movie clips in the bilateral posterior insula, a key area for pain processing and empathy. In contrast, brain responses to others’ pain were reduced in the anterior insula and middle cingulate cortex after negative movie clips. In addition, multivoxel pattern analyses showed that positive emotions enhanced the recruitment of pain-responsive networks, while skin conductance responses were also greater for others’ pain after positive clips, suggesting increased sensitivity to others’ pain in positive emotional states. The reduction of brain responses to others’ pain brain response was counteracted in highly empathetic participants by concomitant enhancement in the medial prefrontal cortex. In a second experiment, we tested the effect of emotions on theory of mind. We used the same emotional movie clips to induce emotions. After each movie clip, participants read stories describing situations where they had to evaluate the belief or emotions of a character. Preliminary results supports the hypothesis that positive emotions facilitate the understanding of others’ thoughts. In a third experiment, we are studying the neural substrate of emotional intelligence by correlating the results of emotional intelligence questionnaires and brain regions volumes. We expect greater volumes in regions such as the medial prefrontal cortex or the anterior insula. Finally, we also showed that positive and negative emotion states induced by movies can produce sustained biases in the perception of (positive or negative) emotional expression in faces.
How to get around backpropagation with unsupervised learning methods

Illing B.

EPFL - BMI

Backpropagation has been the workhorse in machine learning for training deep neural networks ever since its discovery. Since the concept of deep neural nets was inspired by biology, i.e. the layered architecture of the cortex, it is tempting to search for backpropagation-like learning mechanisms in the brain. However this idea was questioned already early and backpropagation was mainly accepted to be biologically implausible. Nevertheless, there is a recent revieval in terms of biologically plausible deep learning algorithms.

Here, we are studying pattern classification by using different unsupervised learning techniques to train the lower layers of a deep net to obtain useful hidden representations of the input. Supervised, backpropagation-like learning is then only used in a shallow classifying output layer. Both can be interpreted as forms of generalized Hebbian learning, being consistent with biological principles of learning.

First results show that a layer of unsupervised learned weights can improve the performance of the shallow classifier. Surprisingly, random feedforward weights to a hidden layer perform almost as good as elaborate unsupervised learning schemes.

An interesting direction to move on is the investigation of stacked autoencoders as unsupervised learned layers. The numerous architectures and algorithms resulting from the use of autoencoders are likely to increase the model’s performance and its capability to describe different learned levels of abstraction. Together this might be giving a novel model of how the cortex learns different difficult tasks using the same architecture, without making use of backpropagation.
Combining predictions and neural oscillations: A speech perception computational model

Hovsepyan S., Olasagatsi I., Giraud A.-L.

UNIGE - Campus Biotech

The seminal paper by David Poeppel and Anne-Lise Giraud indicates the possible link between neural oscillations and speech processing in the brain. Coupled theta and gamma oscillations segment speech into syllable-like units and organize gamma activity into stimulus-induced and theta-modulated decipherable spike trains. On the other hand, during speech perception, the notion of top-down control is a determinant factor. While each framework finds support in modeling studies, it is still very little known how they can cooperate.

We address this question at the theoretical level by creating a neurocomputational model of speech perception to analyze continuous speech. Model features coupled theta and gamma oscillation and is based on the predictive coding framework. Internal representations of the model are limited to the duration and spectral content of syllables that may occur in the input sentence. During inference process, the model identifies syllables presented in the input sentence in an online manner.

The aim of the project is to understand what is the role of theta oscillations and theta-gamma coupling in a scenario where the model already has top-down information both in the temporal and spectral domain. To do so, we compared the performance of the model with and without theta oscillations.

Results show that a model without theta oscillations can track syllable onsets and accurately identify them. However, the model with theta oscillations performs better, as now, syllable onset detection is more accurate and based on the temporal information extracted by theta oscillations from the speech envelope.
Development

Canonical Wnt signalling regulates dendritic arbor development of layer II pyramidal neurons in the rat retrosplenial cortex

Viale B.¹, Constantin L.¹, Petrenko V.¹, Bocchi R.¹, Contestabile A.¹, Salmon P.¹, Kiss J.¹

UNIGE - CMU¹

Dendritogenesis and synaptogenesis are key events of neuronal circuit formation that are finely regulated in time by a multitude of signalling pathways. Several neurodevelopmental disorders arise from an imbalanced neuronal network, which can be consequence of deregulated dendritic and synaptic formation. In particular, retrosplenial cortex (RSC) dysfunction has been linked to bipolar disorder, schizophrenia and autism. Here, using a combination of in utero electroporation and iontophoretic injection, we investigated the role of canonical Wnt signalling in dendritic development and spine formation of layer II cortical pyramidal neurons in the rat RSC. We found that canonical Wnt signalling level increases at the beginning of dendritogenesis and is required for the development of proper dendritic arborization. Disruption of the signalling pathway during a specific, early postnatal time window results in defective dendritic formation that is irreversible and persists until adulthood. At later time points, Wnt signalling is not necessary for maintaining a correct dendritic arborization, however Wnt LOF results in decreased spine and synapse densities. We identified neurotrophin-3 (NT3) as a new downstream target of Wnt pathway, the overexpression of which rescues both dendritic arbor defect as well as spine density. Together, these results reveal a role for canonical Wnt signalling in dendritic arborization of layer II neurons in vivo and suggest a function in RSC circuit formation.
Identifying molecules underlying the glomerular targeting specificity of recently-evolved Drosophila olfactory sensory neurons populations.

Armida J.\(^1\), Arguello J.\(^1\), Abuin L.\(^1\), Benton R. \(^1\)

UNIL-CIG\(^1\)

During the development of the Drosophila olfactory system, olfactory sensory neurons (OSNs) expressing the same receptor elongate their axons towards specific glomeruli within the antennal lobe (AL). Each glomerulus can be easily identified by size, position and shape, making the AL a powerful system for the study of neural map formation. Several molecules have been described as key factors for AL patterning, although these studies have almost exclusively analysed OSNs expressing Odorant Receptors (ORs). Here we focus on the glomerular targeting of neurons expressing Ionotropic Receptors (IRs) whose afferents are the first to invade the developing AL and pioneer the segregation of other classes of neurons. Of particular interest are OSNs expressing members of a tandem cluster of olfactory receptor genes – IR75a, IR75b and IR75c – which are relatively recently evolved neural pathways. IR75a, IR75b and IR75c have segregated their expression into three distinct OSN populations that project their axons to adjacent glomeruli. We aim at discovering the mechanisms underlying these subtle targeting differences to give rise to these three distinct olfactory circuits. To identify molecules involved in IR75a, IR75b and IR75c neuron axon targeting, we have performed RNA-Seq analysis of developing and mature antennal tissue, and Targeted DamID (TaDa) of these specific OSN populations. We present results from these methods and show that we can identify putative axon guidance molecules responsible for the differential wiring of IR75a, IR75b and IR75c expressing neurons. We are currently analyzing the most promising candidates by RNAi and classical loss-of-function genetic analysis to confirm their role in circuit wiring. Our results will shed light into the molecular mechanisms underlying the assembly and evolution of neural circuits.
A Role for Erythropoietin Signaling in radial migration of neocortical excitatory neurons

Constanthin P.¹, Contestabile A.¹, Petrenko V.¹, Salmon P.¹, Kiss J.¹

Erythropoietin (EPO) is a cytokine hormone that is required for erythroid differentiation and has been proved neuroprotective in animal experiments and clinical trials. While EPO and its receptor (EPOR) have been detected in the developing brain, the role of intrinsic EPO signaling in brain development remains unknown. Using in situ hybridization, we found that the expression of both ligand and receptor is timely and spatially regulated in the rat somatosensory cortex during corticogenesis. To investigate the functions of intrinsic EPO signaling we electroporated a small-hairpin RNA targeting EPOR in late generated layer IV spiny stellate neurons. This resulted in striking changes in cell distribution pattern with a large number of shEPOR cells accumulating in the intermediate zone. While most control cells in this zone exhibited a bipolar shape, forced expression of shEPOR significantly increased the number of multipolar cells with branched processes. In addition, a large proportion of shEPOR-overexpressing cells displayed a disoriented Golgi apparatus. Confocal time-lapse imaging of cell locomotion in this region also showed that downregulating EPOR expression results in an increased proportion of cells with numerous highly dynamic processes, a decreased migratory speed of these cells and a decreased number of cells entering into the subplate. This impaired neuronal migration resulted in permanent cell misplacement leading to abnormal sensory behaviours later in life. Finally, forced expression of Erk rescued our migratory phenotype, leading to behavioural recovery. Together, these results show that appropriate activity of intrinsic EPO signaling is required for proper radial migration of neocortical excitatory neurons.
Quantitative analysis of the structural development of the monkey entorhinal cortex.

Piguet O.¹, Chareyron L.², Banta Lavenex P.¹, Amaral D.³, Lavenex P.¹

UCDavis³, UNIL¹, UNIFr²

Recent studies have shown that different hippocampal circuits exhibit distinct developmental profiles, which may subserve the emergence of specific “hippocampus-dependent” memory processes. Since the entorhinal cortex is the main interface between the neocortex and the hippocampus, we aimed to characterize its postnatal development in monkeys. Its superficial layers II and III send feedforward projections to the dentate gyrus and the hippocampus, while its deep layers V and VI receive feedback projections from CA1 and the subiculum. Additionally, layer III receives projections from the presubiculum. The entorhinal cortex comprises seven subdivisions characterized by different interconnections with other brain regions, including the hippocampus. We found no differences in neuron number in any subdivisions of the entorhinal cortex between newborn and adult monkeys. However, we found differences in neuronal volumes, which were specific to certain layers and subdivisions. In rostral areas (Eo, Er and Ei), we found no age differences in volume of layer III neurons, but an increase in volume of layer V neurons between birth and adulthood. In caudal areas (Ec and Ecl), we found that the volume of layer III neurons decreased from birth to adulthood, while the volume of layer V neurons increased from birth to adulthood. Our findings suggest: (1) an early maturation of the superficial layers of the entorhinal cortex, the main input pathways to the hippocampus; (2) an early maturation of the projections from the presubiculum to the caudal entorhinal cortex; and (3) a late maturation of the projections originating in CA1 and the subiculum.
Regulation of mitochondria number along the pathway converting proliferating progenitor cells into newborn neurons in the developing retina

Brodier L.¹, Matter J.-M. ¹

UNIGE - Faculté des Sciences¹

Retinal ganglion cells (RGCs) form the optic nerve that sends visual information from the eye to the brain. Adult RGCs are among the most energy consuming neurons in the whole body. The retina represents a good model to study metabolic reprogramming associated with the transition of Atoh7-expressing retinal cells from pre-committed progenitor cells to RGCs. Previous studies suggest that proliferating cells are highly glycolytic while adult neurons use oxidative phosphorylation for energy production. Little is known about metabolic regulation during neurogenesis. Here, we analyzed mitochondria dynamics along the pathway converting progenitors into newborn neurons with a high temporal resolution. Using live and confocal imaging as well as electron microscopy and mitochondrial DNA quantification, we show that mitochondria are initially present in high number in early dividing progenitors. As neurogenesis proceeds, the number of mitochondria dramatically drops in the pool of pre-committed progenitors expressing Atoh7 at low levels. Following this abrupt decrease, the number of mitochondria rises again when cells that belong to this RGC-biased progenitor pool up-regulate Atoh7, become committed to the RGC fate and differentiate. In addition, we show that changes in mitochondria number in those cells does not involve regulation of master mitochondria biogenesis regulators such as PGC1-a, NRF or TFAM, but rather suggest a role for mitophagy that could involve ATOH7. Our study unravels the dynamic and tight regulation of mitochondria abundance in relation with the onset of neurogenesis and cell commitment.
Abstract # 58

PlexinA4 regulates the migration and neocortical allocation of Htr3a-expressing cortical interneurons

Limoni G.\(^1\), Niquille M.\(^1\), Murthy S.\(^1\), Vutskits L.\(^2\), Dayer A. \(^1\)

UNIGE - HUG\(^2\), UNIGE - CMU\(^1\)

During development, distinct subpopulations of interneurons (INs) arise from different micro-regions of the subpallium, specifically the medial and caudal ganglionic eminences (MGE and CGE, respectively) and the preoptic area. The ionotropic serotonin receptor 3A (HTR3A) is selectively expressed in CGE but not in MGE-derived interneurons. Recent work from our lab using calcium imaging and dynamic assays indicated that CGE-derived interneurons increased their response to HTR3A activation during the late phase of cortical plate invasion and that this receptor is required for proper positioning of CGE-derived interneuron subtype in the neocortex. Here we used genetic screening at three different developmental time-points on FACS-isolated CGE-derived INs in Htr3a-ko and wild-type mice to identify Htr3a-dependent genes. Using this approach, we found that the guidance receptor PlexinA4 (PlxnA4) failed to be normally upregulated in CGE-derived INs deleted for Htr3a. Loss-of-function approaches on cortical slices and in vivo indicated that PlxnA4 regulates the migration and neocortical laminar allocation of HTR3A-expressing cortical interneurons. In addition, in vitro experiments revealed that PlxnA4 is required in CGE-derived INs for proper Semaphorin3A (SEMA3A)-mediated signaling. Overall, our results indicate that PLXNA4/SEMA3A signaling regulates CGE-derived INs migration and laminar allocation into the developing cortex.
The effect of music in preterm infants’ brain: a structural neuroimaging investigation

Almeida J.1, Kunz N.2, Lordier L.3, Darque A.3, Lazeyras F.4, Hüppi P.3

HUG - CIBM4, UNIGE - CMU / HUG1, EPFL - CIBM2, HUG3

Preterm birth can result in long-term complications, namely neurodevelopmental disorders, as occurs when human brain is maturing rapidly and hence highly vulnerable to environmental stressors.

Music, an extrinsic multisensory stimulus, triggers distinct neural substrates later implied in learning and socioemotional regulation, modulating neural networks and functions formed early in development and affected by prematurity.

Using diffusion tensor imaging (DTI) to study brain microstructure in vivo, we aimed to assess if music exposition had a positive impact in premature babies’ brain maturation.

MRI with DTI sequence was performed in term-equivalent age preterm (<33 weeks gestational age) newborns exposed to music during neonatal intensive care unit (NICU) stay, as well as in term-equivalent age preterm newborns and full term newborns not exposed to music. Using a template based region of interest (ROI) method, 19 ROIs were drawn manually in the study template and back transformed to each subject space to compute DTI measures.

Results, regarding fractional anisotropy (FA) quantification, considering the average of all ROIs, revealed a significantly higher FA in term newborns in comparison with PTNM, but not a significant different FA between term vs PTM. FA values were higher in all ROIs of PTM vs PTNM, being significantly higher in corpus callosum (cc) genu and acoustic radiations of term vs PTNM, a difference not significant between term vs PTM.

Preterm newborns exposed to music have FA values closer to the term. Music might thus constitute an effective non-invasive early postnatal neuroenhancement intervention to preterm infants during NICU stay.
Role of the schizophrenia-risk gene miR-137 in corticogenesis layer assembly

Tomasello U.¹, Klingler E.¹, DeVevey L.¹, de Juan R.², Borrell V.², Dayer A.¹

Instituto de Neurociencias², UNIGE - CMU¹

A variety of microRNAs are expressed during cortical development and are thought to regulate early steps of cortical circuit assembly. Interestingly, and in an evolutionary perspective, miR-137 may be linked with cortex folding of gyrencephalic mammal species. A microarray performed on the postnatal cortex of the ferret at postnatal day 2 revealed increased expression of miR-137 in the prospective splenial gyrus as compared to the prospective lateral sulcus in three germinal layers of the visual cortex. In addition, in humans, miR-137 may act as a schizophrenia (SZ) risk gene. Here we aim to investigate the role of miR-137 in the development of upper-layer projection neurons (PNs) using a gain-of-function approach. Using in utero electroporation targeting the dorsal pallium at E14.5, miR-137 was overexpressed in progenitors of PNs and its impact on cell cycle dynamics and migration was analyzed at several subsequent embryonic time points. Our results indicate that cell cycle length is increased by miR137 overexpression and that PNs reach the cortical plate prematurely. Analysis at post-natal stages revealed that miR-137 overexpression inhibits layer 4 identity marker RorB, thus promoting a shift in the production of layer 2-3 PNs. Current studies are designed to determine the molecular mechanisms through which miR-137 controls early steps of progenitor dynamics. Overall, this study indicates that the SZ-risk gene miR-137 has a major regulatory role on cortical progenitor cell dynamics and specification.
Dynamics of single word production from childhood to adolescence and adulthood

Atanasova T.¹, Fargier R.¹, Zesiger P.¹, Laganaro M. ¹

UNIGE - FAPSE¹

Changes in mental processes involved in word production and their time-course are likely to occur across the lifespan. Previous studies have shown functional and temporal differences in speech planning processes among school-age children and adults in picture naming tasks (Laganaro et al., 2015), with, in particular, different neural networks in the time window associated to lexical-semantic encoding between 10-13-year-old children and young adults. Our aim is to investigate when and how the youngsters develop an adult-like activation in word production. More specifically, we expect adolescents to show more adult-like EEG/ERP activities where younger children show the involvement of different neural networks as compared to adults. In order to test our hypotheses, we performed an EEG/ERP picture naming experiment with participants from three different age groups (10-13, 16-18 and 20-30). Participants were asked to name pictures aloud as fast and accurately as possible. Preliminary results based on 11 participants per group demonstrate that children show longer production latencies than adults; the process speeds up in adolescents, nonetheless, without reaching adult-like latencies. We found between-group differences in early (150-220 ms) and later (280-330) time windows on stimulus-aligned ERPs. Microstates analyses indicate clear topographic differences between children and adults and evolution occurring during adolescence. These results suggest that in adolescents there are major changes underway, which have not progressed to be fully adult-like yet. Future studies should be dedicated to the identification of the moment when this process actually becomes adult-like and the exploration of further modifications at advanced ages.
Neuronal activity results in the release of K+ into the extracellular space (ECS), which is rapidly taken up and redistributed via a number of homeostatic mechanisms, including the astrocytic syncytium. In order to assess the interplay between extracellular K+, glial behaviour, and neuronal activity, measuring extracellular K+ ([K+]o) is of fundamental importance. Classically, measurements of [K+]o are carried out using K+ sensitive microelectrodes, which only provide a single point measurement of an undefined spatial resolution. Using an imaging approach could open the door for spatiotemporal mapping of [K+]o-related events. Here we report on the design, characterization, and utilization of a fluorescence imaging-based K+ sensitive nanosensor for the ECS based on dendrimer nanotechnology, also presenting a ratiometric derivative. We validate the nanosensor strategy in brain tissue in response to elicited neuronal activity, correlating this to the extracellular field potential. We then demonstrate underlying spatiotemporal aspects of K+ flux in the brain using this newly developed sensor. Together these experiments demonstrate the efficacy of the K+ sensitive nanosensor design, validate the possibility of creating multimodal optical nanosensors based on dendrimer technology, and shed new light on mechanisms controlling K+ flux in the brain.
Molecular and Cellular Neuroscience

Resolving accumbal projections to lateral hypothalamus

Thoeni S.¹, O'Connor E.², Lüscher C.³

La Roche², UNIGE-CMU³, UNIGE - CMU¹

The nucleus accumbens (NAc) inhibits several downstream brain areas including the ventral pallidum, lateral hypothalamus (LH) and ventral midbrain. Our previous work has shown that NAc medium-sized spiny neurons (MSNs) projecting to LH predominantly express the dopamine D1 receptor (D1-MSNs) and inhibit LH GABA neurons to control food consumption.

Here, using neural tracing and in vitro electrophysiology in transgenic mouse lines that permit identification and optogenetic control of specific cell type we further dissect the connectivity and synaptic plasticity of this pathway.

First, we found that D1-MSN-to-LH projections origin predominantly from anterior parts of the NAc, whereas D2-MSN-to-LH origin mainly from the most posterior part of the NAc.

Second, in addition to inhibition of LH GABA neurons, we found that D1-MSNs also monosynaptically inhibit LH glutamate neurons.

Third, in contrast to NAc projections to the pallidum and midbrain, inhibitory synapses between D1-MSNs and LH fail to show long-term potentiation (LTP) upon high frequency stimulation protocol (HFS) and forskolin (FSK) application. Moreover, the plasticity does not differ depending on the postsynaptic LH GABA or glutamate neuron. Finally, we found that GABAB- and CB1-receptor activation depressed the synapse, whereas low frequency stimulation protocol does not.

Taken together, our data challenge the traditional view of direct and indirect pathways as applied to ventral striatal circuitry and suggest distinct properties of NAc-to-LH inhibitory synapses that may be critically involved in the control of motivated behavior.
Effects of dCYFIP dysregulation in behavior and synapse functionality

Mariano V., Kanellopoulos A., Vannelli A., Bagni C.

UNIL-DBCM

The most frequent form of inherited intellectual disability (ID) and autism is the Fragile X Syndrome, caused by the absence of the RNA binding protein FMRP. Individuals with FXS display a range of developmental and behavioral deficits with mild to severe ID, attention deficit disorder (ADHD) and autism spectrum disorders (ASD).

The cytoplasmic FMRP-interacting protein 1 (CYFIP1) is among the best characterized FMRP interactors. In neurons CYFIP1 is involved in two molecular processes crucial for synaptic development and functionality. The CYFIP1-FMRP complex regulates the translation of FMRP-targeted mRNAs; the CYFIP1-WAVE complex regulates actin remodeling. Consequently, absence of CYFIP1 leads to dendritic spine dysgenesis. Several studies have shown that copy number variation (CNVs) of the CYFIP1 gene are linked to neuropsychiatric disorders such as autism spectrum disorders (ASD), schizophrenia (SCZ), epilepsy and Alzheimer’s disease (AD).

The Drosophila Cyfip is involved in synapse formation and stability, in neuromuscular junction development and axonal branching.

We currently investigate the cellular and molecular functions of dCyfip using different and complementary approaches such as behavioral assays, electrophysiology and microscopy. Flies with dysregulated levels of dCyfip exhibit locomotory and circadian rhythm defects, neuronal branching and phototransduction impairments.

The self-inactivating KamiCas9 system for the editing of CNS disease genes

Vachey G.1, Merienne N.1, de Longprez L.2, Meunier C.1, Zimmer V.1, Perriard G.1, Canales M.1, Mathias A.1, Herrgott L.1, Pythoud C.1, Rey M.1, Pellerin L.3, Brouillet E.2, Perrier A.4, du Pasquier R.1, Deglon N.1

INSERM4, Unil3, CHUV1, CEA2

Neurodegenerative disorders are a major public health problem because of the high frequency of these devastating diseases in the population. Genome editing with the CRISPR/Cas9 system is making it possible, for the first time, to modify the sequence of genes linked to these diseases in the adult brain. Here, a self-inactivating CRISPR/Cas9 system, kamiCas9, was designed for transient expression of the Cas9 protein and high editing efficiency. In the first application of this technology to neurodegenerative disorders, the gene responsible for Huntington’s disease (HD) was targeted in adult mouse neuronal and glial cells. Mutant huntingtin (HTT) was efficiently inactivated in mouse models of HD, leading to an improvement in key markers of the disease. Sequencing of potential off-targets with the constitutive Cas9 system in differentiated human iPS cells, revealed a very low incidence with only one site above background level. Importantly, the off-target frequency was drastically reduced with the kamiCas9 system. These results demonstrate the potential of the self-inactivating CRISPR/Cas9 editing for applications in the context of neurodegenerative diseases.
Cold-Inducible RNA Binding Protein (CIRBP) contributes to REM sleep homeostasis and regulation of locomotor activity

Hoekstra M.\textsuperscript{1}, Franken P.\textsuperscript{1}, Emmenegger Y. \textsuperscript{1}

UNIL-CIG\textsuperscript{1}

The sleep-wake distribution is orchestrated by interacting homeostatic and circadian processes. Besides playing a role in circadian rhythms, clock genes play a role in sleep homeostasis. This claim is partly based on the observation that depriving mice of sleep changes clock-gene expression. What could link sleep pressure to clock-gene expression? We propose that CIRBP could be this link because i) its expression is strongly sleep-wake driven, likely through the sleep-wake dependent changes in brain temperature, and ii) CIRBP is necessary for high-amplitude clock-gene expression. We hypothesize that sleep-wake dependent changes in clock-gene expression are attenuated in Cirbp knock-out (KO) mice, thereby altering the sleep homeostat.

To test this, we assessed sleep-wake regulation and gene expression in KO and wild-type (WT) mice during baseline, sleep deprivation (SD; between ZT0-6) and recovery conditions. EEG/EMG recordings were used to quantify sleep-wake state and brain activity, passive infrared-sensors to quantify locomotor activity, and qPCR to quantify gene expression in cerebral cortex and liver. Throughout the experiment, KO mice were more active and displayed an altered sleep-wake distribution resulting in higher sleep pressure, as measured by NREM sleep EEG delta power (1-4Hz). Moreover, KO mice were deficient in compensating for the loss in REM sleep time incurred by the SD. Although several transcripts differed, we found no evidence that CIRBP alters the SD-induced changes in clock-gene expression. Our findings indicate that although CIRBP plays a role in the sleep-wake distribution, activity, and REM sleep homeostasis, alternative signaling pathways underlie the SD-induced changes in clock-gene expression.
Defining mitochondrial biomarkers and function using magnetic resonance spectroscopy at 14.1 Tesla in a mouse model of mood disorders

Cherix A.1, Donati G.1, Lizarbe B.1, Lei H.1, Cardinaux J.-R.1, Gruetter R.1

EPFL - Other1

In vivo magnetic resonance imaging (MRI) and spectroscopy (MRS) are two non-invasive techniques of choice for investigating and monitoring brain metabolic and biological changes related to mitochondrial function and health. Mitochondria have been associated with many brain disorders and, among them, mood disorders. Defining and understanding mitochondrial MRI/MRS biomarkers related to mood disorders could be an important contribution for a better endophenotypic characterization of these psychiatric illnesses.

In this study we have investigated the MRI/MRS profile of a new mouse model of mood disorders lacking an important brain plasticity gene, Crtc1 (CREB-regulated transcriptional coactivator 1).

Metabolic alterations were determined with T2-weighted MRI together with 1H-MRS of prefrontal cortex (PFC) and dorsal hippocampus (HDors). Results indicated an age-dependent alteration of glutamate and GABA levels in Crtc1 KO mice PFC together with a constant reduction in phosphocreatine (PCr) energy metabolites in the dorsal hippocampus (PFC: Glu(-12±3%), GABA(-26±11%; HDors: PCr(-20±8%)). qPCR experiments revealed no changes in electron transport chain (ETC) gene expression but increased creatine kinase (CKMt and CKB) levels in the dentate gyrus of KO mice, confirming neuroenergetic deficiency in dorsal hippocampus. Mitochondria quantification using mtDNA copy number revealed a specific reduction of mitochondrial mass in the dentate gyrus, which could explain the observed energetic dysfunction. Finally, 1H[13C]-MRS results upon infusion of [U-13C]glucose suggested metabolic differences in the dorsal hippocampus, where enrichment curves indicate a reduced glucose uptake or an increased glycolytic rate in KO animals. These results suggest that CRTC1 might be an essential regulator of brain energy metabolism in the mouse dorsal hippocampus.
Astrocytic mitochondrial impairments in an animal model of schizophrenia

Zehnder T.¹, Gogos J.², Bezzi P.¹

UNIL-DNF¹, Columbia University²

One of the main candidate risk gene for behavioural phenotype of 22q11 deletions syndrome (22q11DS) is the gene encoding for proline dehydrogenase (PRODH), a mitochondrial enzyme involved in the metabolism of L-proline. The expression of PRODH is typically ascribed to proliferating tissues (Polyak et al., Nature, 1997) where it regulates cell proliferation (Donald et al., Cancer Res, 2001) and metabolism (Liu et al., PNAS, 2012). The functional role of PRODH in the brain is not completely understood. We and others have found that PRODH expression in the brain is particularly high during postnatal development, the temporal period commonly associated to gliogenesis (Bandeira et al., PNAS, 2008). Interestingly, we also found that PRODH expression in the astrocytes seems to be enriched into the prefrontal cortex (PFC), one of the brain main area associated to cognitive processes. We also found that these astrocytes, similar to the proliferating cells, undergo a progressive activation of oxidative phosphorylation (OxPho) during postnatal maturation, a situation that could render developing astrocytes more susceptible to mitochondrial perturbations (Fulda et al., Nature Rev Drug Disc, 2010). In astrocytes of PRODH deficient mice (Paterlini et al., Nature Neurosci., 2005), the activation of OxPho is perturbed and both the respiratory capacity and the ATP levels were significantly impaired. We concluded that PRODH expression during postnatal development is necessary to maintain a proper mitochondrial function. In the near future we plan to investigate the effect of PRODH and OxPho impairments on the postnatal maturation of astrocytes in terms of cellular proliferation and integration into the network.

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Transcriptional Control over Cortical Progenitor Plasticity

Oberst P.

UNIGE - CMU

The cerebral cortex is the seat of our voluntary sensory-motor processing abilities, higher cognitive functions and consciousness. At the core of its intricate working abilities is the fine-tuned organization of distinct neuronal subtypes into sophisticated cortical circuits. The cortex is organized into 6 horizontal layers, which are comprised of specific neuronal subtypes with distinct projection patterns, morphological features and gene expression profiles. Although highly heterogenous, the distinct neuronal subtypes are produced from a seemingly homogenous population of progenitor cells during development. Using a variety of techniques, including embryonic surgeries and transcriptional profiling, I am studying how cortical progenitors can give rise to distinct neuronal subtypes in a temporal manner.
Transcriptome Profiling of Vomeronasal Sensory Neurons using Single-Cell RNA-Sequencing.

Fodoulian L.¹, Tuberosa J.², Carleton A.³, Rodriguez I.²

UNIGE - Faculté des Sciences², UNIGE - Faculté des Sciences & CMU¹, UNIGE - CMU³

In mammals, sensory neurons residing in the vomeronasal organ (VNO) mediate the detection of pheromones and kairomones. Each of these cells expresses a single chemoreceptor gene, chosen out of a large repertoire. Despite the important role played by the vomeronasal system in social interactions, but also in predator and sick conspecific avoidance, very little is known about the specific identities of vomeronasal sensory neurons (VSNs). Here, we used single-cell RNA-sequencing to profile 458 mouse VSNs. Using an unsupervised graph-based clustering approach, we identified 2 main neuronal populations. Each of these two groups expresses either the G protein subunits Gao or Gai2, among a large set of specific markers. Our analysis also identifies still undescribed subpopulations of Gai2-expressing VSNs, which interestingly do not correspond to populations functionally defined by the chemoreceptor they express.
Neurological or Psychiatric Conditions

Disinhibition of VTA dopamine neurons drives heroin reinforcement.

Corre J.¹, Pascoli V.², Luscher C. ³

UNIGE-CMU², UNIGE-CMU-HUG³, UNIGE - CMU¹

The “dopamine hypothesis”, proposed in the 1980s, states that the defining commonality of addictive drugs is an increase of mesolimbic dopamine levels, which reinforces self-administration eventually leading to addiction. While much recent evidence supports this hypothesis, it has been challenged for opioids. For heroin in particular, the involvement of dopamine in the reinforcing properties remains controversial, especially for the initial phase of heroin exposure before dependence is established.

Here we confirm the reinforcing properties of heroin with a self-administration (SA) model in mice. To probe a model of disinhibition, we performed inhibition and occlusion experiments using chemogenetic, optogenetic manipulation of neural activity together with heroin self-administration. When VTA DA neurons were inhibited by a DREADD, heroin SA could not be established. Likewise, the optogenetic self-stimulation (SS) of VTA DA neurons was occluded by heroin in a dose-dependent fashion. Finally we show that heroin occludes reinforcement of self-inhibition of VTA GABA neurons infected with Arch3.0.

All together these results show that mesolimbic DA transmission plays a crucial role in the reinforcing properties of opioids. The data confirm a disinhibitory mechanism whereby heroin targets GABA neurons that then leads to an increase of DA neurons activity. This scenario applies from the very early stage of drug exposure and not only when opioids intake has become chronic and the mice are dependent.
Cortical morphology development in patients with 22q11.2 deletion syndrome at ultra-high risk of psychosis

Padula M.¹, Schaer M.², Armando M.², Sandini C.², Zoeller D.³, Scariati E.², Schneider M.², Eliez S.²

UNIGE - Faculté des Sciences¹, EPFL - UNIGE³, UNIGE - Faculté de Medecine²

Patients with 22q11.2 deletion syndrome (22q11DS) present a high risk of developing psychosis. While clinical and cognitive predictors for the conversion towards a full-blown psychotic disorder are well defined and largely used in practice, neural biomarkers do not yet exist. However, a number of investigations indicated an association between abnormalities in cortical morphology and higher symptoms severities in patients with 22q11DS. Nevertheless, few studies included homogeneous groups of patients differing on their psychotic symptoms profile. In this study, we included 22 patients meeting the criteria for an ultra-high risk (UHR) psychotic state and 22 age, gender and IQ-matched non UHR patients. Measures of cortical morphology, including cortical thickness, volume, surface area and gyrification, were compared between the two groups using mass-univariate and multivariate comparisons. Furthermore, the development of these measures was tested in the two groups using a mixed model approach. Our results showed a pattern of increased and reduced cortical volume and surface area in UHR patients compared to non UHR. In particular, altered surface area predicted changes with age in global functioning scores. We also observed accelerated cortical thinning during adolescence in UHR patients with 22q11DS. These results, although preliminary, suggest that alterations in cortical volume and surface area as well as altered development of cortical thickness may be associated to a greater probability to develop psychosis in 22q11DS.
Does cerebellar dysfunction contribute to tremor in Parkinson’s disease?

Batzianouli E.¹, Pagliaro M.¹, Benninger D. ¹

CHUV¹

Background
Rest tremor in Parkinson’s disease (PD) is disabling and responds often incompletely to conventional therapy. The pathogenesis remains largely unknown. Functional imaging, neurophysiology and structural studies, and stereotactic surgery point to an involvement of the cerebellum and the cerebello-thalamo-cortical pathway, but the precise nature remains unknown. These functional changes in the cerebellum may include pathological and compensatory mechanisms.

Objective
This study aims to investigate the potential role of cerebellar dysfunction in the pathogenesis of tremor in Parkinson’s disease (PD).

Methods
Cerebellar function can be tested by the eyeblink classical conditioning (EBCC), a form of associative motor learning, which depends on the integrity of the cerebellum and the olivocerebellar circuit. Fifteen PD patients with tremor (PD+tremor) and fifteen without (PD-tremor) were investigated compared to age-matched healthy controls. We assessed the associative motor learning in a delayed classical conditioning paradigm.

Results
Our findings suggest an impaired EBCC both in the PD-tremor and PD+tremor compared to healthy controls, which do not differ regarding tremor. The rate of associative motor learning ranges widely from being preserved to complete abolition which appears to correlate rather with the disease progression.

Conclusion
There is an impaired associative motor learning in PD suggesting a potential cerebellar dysfunction, which does not contribute to tremor pathogenesis. This cerebellar dysfunction may progress along with the neurodegenerative process in PD, which needs to be further explored.
Novel Sliding-Window approach reveals deviant developmental trajectories of structural covariance in 22q11.2 Deletion Syndrome

Sandini C.

Schizophrenia is currently considered to arise from a neurodevelopmental disorder of connectivity. However up to now few studies have investigated connectivity development longitudinally in patients at risk for psychosis. 22q11.2 Deletion Syndrome is a powerful model to investigate the pathogenesis of psychosis in a neurodevelopmental perspective. Structural covariance is an alternative method of exploring connectivity among brain regions. Networks reconstructed from structural covariance have disrupted architecture in patients suffering from psychotic symptoms both in the general population and in 22q11DS. However to date but little is known about how SC network architecture matures in patients at risk for psychosis. Here we implement a novel sliding window approach to precisely characterize development of SC network architecture in a large longitudinal cohort of patients with 22q11DS and a corresponding group of healthy controls. Our result demonstrate aberrant maturational trajectories of Structural Covariance with disturbed architecture previously linked to psychosis selectively emerging during adolescence. Patients also presented a lack of typical network development during late-childhood, that was furthermore particularly striking for frontal connectivity.
Evaluation of Redox Dysregulation in the Pathology of Schizophrenia Using Induced Pluripotent Stem Cell Technology

Giangreco B.¹, Steullet P.¹, Cabungcal J.-H.¹, Bartesaghi L.², Toni N.³, Chrast R.², Do K.¹

Karolinska Institutet², DNF³, CNP/CHUV¹

Schizophrenia (SZ) is a disorder that involves genetic and environmental factors. A decrease of glutathione (GSH), a major cellular antioxidant, was shown in patient’s brain and CSF. Furthermore, polymorphisms in the key synthetizing enzyme for GSH were found associated with the disease. These observations lead to the hypothesis that redox dysregulation is a main hub in this disorder. In this study, we set up a method based on fluorescence imaging to identify the redox state of thiol residues in a GSH deficient mouse model (Gclm⁻/⁻). Our long-term objective is to use induced pluripotent stem cells (iPSC) to examine the impact of oxidative stress on neurons derived from a well-characterized cohort of SZ patients. We established the conditions for thiol labelling by fluorescence in WT mice brain slices and evaluated its sensitivity. Then, we investigated redox state of cells in WT and GBR-treated Gclm⁻/⁻ mice, GBR being a dopamine reuptake inhibitor that induces additional oxidative stress. In parallel, we have started to generate iPSC from patient’s fibroblasts and to derive them into neurons. The ratio between oxidized and reduced thiols was increased in GBR-treated Gclm⁻/⁻ compared to WT mice, suggesting a more oxidized cellular environment. This ratio will be measured in iPSC-derived neurons from patient’s fibroblasts that we are currently producing. This method together with other approaches will allow to assess whether the redox state is also altered in iPSC-derived neurons from patients. Ultimately, application of this method to iPSC may pave the way to individualized therapies.
Implicit self-other discrimination affects the interplay between multisensory affordances of mental representations of faces

Zeugin D.¹, Arfa N.², Notter M.², Ionta S.³, Murray M.²

SeMoLa-LINE-CHUV³, LINE-CHUV², UNIL-DBCM¹

Identifying people based on face recognition is an apparently simple but, in fact, complicated ability. We are able to distinguish ourselves from others based on the integration of face-related multisensory (and motor) cues. Understanding how identity attribution relies on plastic interrelations between different sensory inputs might open new avenues on the neuropsychological basis of self-other distinction. Here we used the Face Inversion Effect (FIE) - a specific bias in mentally process (rotate) images of faces, opposed to inanimate objects - to assess the differential impact of vestibular and biomechanical constraints on mental rotation of images of self- versus other-faces. Response times (RTs) from 20 participants showed that the FIE was stronger for self-face than other-face images, i.e. greater modulation of RTs for self-face than other-face images, as a function of the image orientation. These data suggest the existence of distinct identity-based mechanisms to mentally process self- versus other-face representations. On this basis, we provide evidence that, to represent faces, the relative weight of somato-vestibular input can vary according to identity.
Neuron-glia interactions

3D calcium imaging provides a novel view on astrocyte biology

Bindocci E.¹, Savtchouk I.¹, Liaudet N.¹, Becker D.¹, Carriero G.³, Volterra A.¹

UNIL-DBCM¹

Astrocytic calcium activity has been proposed to play a role in several brain processes, notably regulation of blood flow and high-level integration of neuronal signals, but methodological restriction to conventional 2D microscopy has limited so far a comprehensive understanding of its biological features. Indeed astrocytes are highly three-dimensional cells, characterized by a high level of structural and functional complexity that cannot be fully appreciated by looking at a single focal plane at the time. Combining advanced technologies such as fast-scanning 2-Photon systems and transgenic mouse lines expressing the calcium indicator GCaMP6f specifically in astrocytes, in the present study (Bindocci et al, Science 2017) we were able to record 3D calcium activity from entire astrocytic territories (about 30 focal planes) and reconstruct, for the first time, activity maps of both optically resolved (core) and sub-resolved (gliapil) astrocyte regions in brain slices as well as awake mice. Using this superior methodological approach, we found astrocytic processes to be the most active compartment of the cell, followed by endfeet and eventually cell body. The latter was very infrequently active. Most activity in processes and end-feet was local and fast and showed alternation of small hot spots and cold regions. Part of the process activity was TTX-sensitive. Overall, our 3D data show a high level of compartmentation in astrocyte function, pointing to local modulatory actions. Therefore, classical studies of astrocyte-synapse or astrocyte-blood vessel interaction, mostly based on cell body Ca2+ measures, do not represent the real biology of such interactions, which needs to be re-studied shifting significantly spatial-temporal scales.

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Investigating the territorial nature of astrocyte-synapse interactions in the hippocampus

Mergiya T.¹, Savtchouk I.¹, Volterra A. ²

Andrea.Volterra@unil.ch², UNIL-DNF¹

Astrocytes interact with neurons to modulate synaptic signaling and plasticity. Using an advanced 3D Ca2+ imaging technique, our lab recently revealed that astrocytes respond to (minimal) electrical axonal stimulation of medial perforant path (MPP) axons in adult hippocampal slices with a time-correlated Ca2+ elevation in a tiny spot (Bindocci et al, Science 2017). It was, however, challenging to visualize all recruited fibers within the astrocytic territory. We therefore aim at stimulating only ChR2 positive fiber(s) using optogenetics. To this end, MPP fibers from entorhinal cortex neurons infected with ChR2-tomato virus were focally activated by blue light. Upon photostimulation, LFP proportional to laser power and ChR2 expression level were recorded in acute brain slices. Neuronal or astrocytic Ca2+ dynamics upon ChR2 stimulation were also monitored via 2P imaging via the Ca2+ indicator (GCaMP6f) expressed in granule cells or astrocytes. We first validated the efficacy of neuronal GCaMP6f in reporting a xonal activity by showing that GCaMP6f-positive neuropil underwent a time-correlated Ca2+ elevation following electrical stimulation of MPP (Bindocci et al, Science 2017). Next, Ca2+ dynamics in neuropil and gliapil will be investigated following ChR2 activation to achieve a single axon photostimulation. Astrocytes in the middle or outer dentate molecular layer will then be manipulated to probe the territorial segregation of the astrocytic modulation in distinct synaptic territories of a granule cell after stimulation of MPP or LPP.

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Metabolite correlates of the positive and negative BOLD responses during visual stimulation

Boillat Y., Xin L., Van der Zwaag W., Gruetter R.

EPFL, Spinoza Center, NL, EPFL - Other

An increase of the positive BOLD signal has been used as a “proxy” to detect an increase in neuronal activity. However, a negative BOLD response has also been observed in different circumstances (e.g. visual stimulations with small circular checkerboard) and is thought to be mostly linked to inhibitory activity. The origin of such a BOLD response is still not clear and our aim was to investigate it by looking at the metabolic changes using functional magnetic resonance spectroscopy at 7T (fMRS). Two groups were scanned at 7T: one for the positive BOLD (8 participants) and one for the negative BOLD (9 participants). An fMRI acquisition was acquired followed by an fMRS sequence. A visual stimulation was performed with a full screen radial checkerboard (positive BOLD; STIM) or a small checkerboard ring (negative BOLD; STIM) and a gray screen (REST) for both fMRI (10s STIM–20s REST x 12) and fMRS (2min REST followed by 5min STIM and REST x 2). During a stimulation triggering a positive BOLD response, glutamate significantly increased and a trend for a lactate increase was observed. During the negative BOLD response, a decrease of GABA compared to baseline was observed with a trend for a decrease of glutamate/glutamine. In addition, higher GABA concentrations at baseline seem to correlate with a higher negative BOLD amplitude. Although more participants are being acquired, the preliminary results suggest that the positive BOLD is linked to glutamatergic (excitatory) activity and the negative BOLD to GABAergic (inhibitory) activity in the visual cortex.
The role of glyco
gen derived lactate in cocaine-related memories.

Boury-Jamot B.¹, Carrard A.¹, Halfon J.-L.¹, Halfon O.², Magistretti P.³, Boutrel B. ²

CNP/KHAUST/EPFL³, CNP/CHUV¹, SUPEA/CHUV²

Drug memories that associate contextual cues with the effects of drugs are known to shape persistent drug seeking behaviors in rodents. We explored the possibility that disrupting glycogenolysis in the basolateral amygdala (BLA) could impair the acquisition and maintenance of memories associated with cocaine cues. We have observed that rats treated with intra−BLA infusions of the inhibitor of glycogen phosphorylase, 1,4-dideoxy−1,4-imino−D-arabinitol (DAB 300pmol/side), 15min before conditioning sessions of a conditioned place preference (CPP), failed to exhibit a clear cut preference for side previously paired with cocaine. A double post conditioning injection of DAB (15min before and 5h after a re−exposure to the context) abolished the cocaine attractiveness for up to two weeks. We then targeted the prefrontal cortex (PFC) with a similar protocol, but rats continued to exhibit a strong preference for the cocaine compartment. However, recent evidence established that consolidation of drug reward memories depended on successive phases, with the BLA involved in the early phase and the PFC possibly involved in the late phase of memory consolidation. Rats were injected with DAB (480pmol) into the PFC 15min and 12h after the contextual re−exposure. In contrast to rats injected with DAB 15min/5h, those treated 15min/12h exhibited a significantly reduced exploration of the cocaine compartment. Taken together, these results give a pointer to a signaling role of lactate in both acquisition and maintenance of cocaine−seeking behavior following a BLA−PFC temporal pathway and open novel therapeutic avenues to reduce the long−lasting impact of drug cues on conditioned responses to cocaine.
Potassium channels in dorsal horn microglial cells after spared nerve injury

Gattlen C.

CHUV

Nerve injury induces hyperexcitability through action potentials which sensitize the neurons in the dorsal horn of the spinal cord. Microglia activation appears during this sensitization process and enhances it by the release of cytokines and chemokines. As a result, the nociceptive pathways are amplified and provoke hypersensitivity and allodynia. In this study we investigate how potassium currents from microglial cells are modified in culture and spinal cord (SC) slices after the spared nerve injury (SNI) model of neuropathic pain.

Two days after SNI the resting membrane potential (RMP) of microglial cells in culture was -29.73 ± 2.96 mV. In sham 2 days: -20.00 ± 2.40 and naive conditions: -16.77 ± 1.89 mV. The potassium currents recorded from microglial cells in culture in naive conditions at -160 mV: -43. ± 6.19 were significantly smaller than the currents recorded 2 days after SNI: -84.55 ± 8.82 mV. In SC slices the RMP was -35.86 ± 6.33 mV, n=8 in naive conditions and 2 days after SNI was -29.27 ± 10.57 and 2 days after sham was -15.19 ± 2.37 mV. In slices there is no difference between the potassium currents at -160 mV in naive conditions: -18.05 ± 4.59 mV and sham 2 days: -10.39 ± 2.55 or SNI 2 days: -16.66 ± 4.84 mV. The qPCR shows mRNA increase for the inward rectifying potassium channel Kir2.1 7 days after SNI.

Our results indicate a possible change in potassium channels after SNI but additional experiments are necessary.
Recovery of reaching and grasping ability is crucial for rehabilitation from cervical spinal cord injury (SCI). Epidural electrical stimulation (EES) is a promising technique for limbs motor control improvement after SCI in various animal models and in humans. In particular, spatiotemporal alternation of stimulation bursts during movement restored skilled locomotion in rats and Rhesus monkeys with SCI and such refined stimulation protocols could be pivotal also for the recovery of functional reaching and grasping movements. In fact, upper limbs control requires coordinated and synergistic muscle activation that would be difficult to achieve with simple continuous stimulation protocols.

In order to design spatiotemporal cervical epidural stimulation protocols, we analyzed the activation patterns of motor-pools in the cervical spinal cord during a reaching and grasping task in a Macaca fascicularis monkey. The monkey executed repeatedly a drawer opening task, while electromyographic (EMG) activity was recorded from eight arm and hand muscles. Intra-movement phases were detected from EMG activity in order to differentiate between limb flexion, limb extension and grasp phases. Muscle activity was then projected to the corresponding spinal cord segments by means of a motoneuronal map established in literature, allowing to extract spinal cord spatiotemporal activation maps. The spatiotemporal maps highlighted well defined spatially and temporally specific motoneuronal activations and were reproducible across sessions performed on different days. Based on such results we propose a simple spatiotemporal stimulation protocol mimicking the natural synergistic muscle activation during upper limb movements.
Reaching for water: a novel cortex dependent forelimb task for mice

Bonardi C.

UNIGE - CMU

Cutting edge genetic and optical tools to study neural circuits in mice only gain their full potential in combination with well-controlled behavioral paradigms. In rodent motor research, the “reach-to-grasp” behavior has proven to be a powerful paradigm because it closely resembles that of primates and it has been well characterized in the context of stroke and Parkinson’s disease. However, the classical reaching for food pellets in rodents also has some technical shortcomings (e.g. limited number of trials) and its use under head-fixed conditions is rather limited.

We explore a novel version of this paradigm in which mice are trained to reach for water droplets instead of food pellets. We found that freely moving mice immediately engage in this water droplet reaching task, performing hundreds of reaching trials per hour.

Inspired by the classical “center-out” reaching task in primate, we next investigated whether mice were able to perform the task under head-restrained conditions and towards different target locations. We found that head-restrained mice can rapidly learn to locate, reach out and grab water drops presented in different target locations around their snout. Interestingly, not the whiskers, but the olfactory system is principally used for target localization. Optogenetic inactivation of the motor cortex halted the initiation, as well as the execution of ongoing reaching movements.

Taken together, we found that reaching for water has the potential to become a universal and flexible behavioral platform for systems neuroscience research in mice.
A new protocol to derive human retinal pigment epithelium from pluripotent stem cells and its evaluation as an in vitro gene therapy model

Udry F.¹, Decembrini S.³, Kostic C.¹, Gamm D.², Arsenijevic Y. ³

University of Wisconsin², UNIL-JGEH¹

The neural retina activity relies on retinal pigment epithelium (RPE) functions and its deficiency give rise to several diseases, of which most of them result in visual impairments or blindness. The ability to generate hRPE for disease modelling, drug screening or transplantation is particularly worth to answer these important challenges. Here we present an easy, reliable, and serum-free method to generate hRPE from induced pluripotent stem cells (iPSCs) in culture.

Starting from feeder-free culture conditions we established a simple three-step protocol able to induce pigmented foci as early as 18 days after differentiation. iPSC-RPE cells exhibited pigmentation and cobblestone-like morphology and expressed mRNAs of typical RPE markers such as RPE65 (visual cycle), MERTK (phagocytosis), BEST1 (ion homeostasis), ZO-1 (tight junctions) or OTX2 (transcription factor). Protein presence of some of these markers was assessed by immunohistochemistry and phagocytosis assay showed slow kinetics of POS internalization. Electron microscopy revealed polarized iPSC-RPE cells and PEDF and VEGF secretion level ranged in commonly reported values. Finally, RPE cells were infected with lentivirus bearing different constructs as an insight into iPSC-RPE cells response to lentiviral-based gene therapy.

In conclusion, the presented protocol provides a quick and consistent method to generate hRPE from pluripotent stem cells that revealed to be a suitable model for in vitro gene therapy. By combining a CRISPR approach to mutate hiPSCs line and our RPE differentiation protocol, we aim at producing in vitro model for RPE deficient-induced retinal diseases to test lentiviral-based gene therapies.
Structural correlates of neuroprosthetic learning

Philippides A.

UNIGE - CMU

Structural correlates of neuroprosthetic learning

Brain-Machine-Interfaces (BMI) can potentially provide powerful means to replace impaired motor functions. To improve the current devices it is important to gain a better understanding of the neuronal mechanisms underlying neuroprosthetic control. We have recently demonstrated that learning related changes in neuronal firing can be highly specific to the conditioned neuron. These changes are most likely the result of neuronal plasticity such as long term potentiation or more synchronous input to the conditioned neuron. Since changes in size of the dendritic spines can be good indicators of the synaptic plasticity, we expect to observe a more extensive reorganization along the dendrite of the conditioned, as compare to the neighboring, non-conditioned neurons. To track structural changes related to neuroprosthetic learning we designed a novel multiple focus two-photon microscope able to simultaneously track structural and functional changes across several layers. We will present our first results combining structural, functional and behavioral data during neuroprosthetic learning.
A wireless brain-spine interface alleviating gait deficits after Parkinson’s disease in primates

Raschella F., Milekovic T., Schiavone G., Capogrosso M., Micera S., Courtine G., Lacour S.

Levodopa and deep brain stimulation alleviate most of the symptoms associated with Parkinson’s disease. However, axial gait disorders are less responsive to these treatments. These deficits include short and slow steps, balance deficits and freezing of gait that involves episodes during which the affected persons are not capable of initiating locomotion.

Over the past decade, we have established a mechanistic and technological framework that guided the design of electrical spinal cord stimulation protocols engaging extensor and flexor muscle groups. We created an interface between the leg motor cortex activity and these spatially selective stimulation protocols, so as to engineer a brain–spine interface – a neuroprosthetic system that reinforced intended movements. As early as 6 days after spinal cord injury, this brain–spine interface restored weight-bearing locomotor movements of the paralyzed leg in nonhuman primates. Here, we show that the brain-spine interface effectively alleviates axial gait deficits observed in Parkinson’s disease. These experiments were conducted in MPTP-treated Rhesus macaque monkeys, which is the gold model to reproduce Parkinson’s disease symptomatology. After MPTP treatment, a rhesus macaque was implanted with the wireless brain-spine interface. Brain recordings of the left and right leg motor cortex were used to detect neural states related to flexion and extension movements of both legs while the animal walked freely overground or over a horizontal ladder. The detection of these gait events controlled an implanted pulse generator that delivered electrical stimulation through two e-dura electrode array implants that covered the dorsal aspects of the lumbar and sacral spinal cord.
Functional Organization of the Visual Cortex of Microcebus Murinus

Ho C.1, Zimmermann R.1, Weidinger J.2, Pifferi F.3, Wolf F.2, Aujard F.3, Huber D. 4

UNIGE -CMU⁴, Max Planck Institute for Dynamics and Self Organization², CNRS - MNHN³, UNIGE - CMU¹

The prosimian mouse lemur (Microcebus murinus) is one of to the World’s smallest primates (~60gr). They are nocturnal but highly visual animals foraging, and hunting insects in Madagascan forests. Despite its developed its visual system allowing it to navigate in dense branch systems in dim light, little is known about how its visual cortex processes information functionally. Current research has shown two main types of orientation representation in visual cortex across different species – random ‘salt and pepper’ in rodents or organized ‘pinwheel maps’ in carnivores and primates. In the mouse lemur, it is uncertain whether its visual cortex contains organized maps due to its small size. Using cutting-edge systems neuroscience tools adapted from rodent research, we investigate the functional organization of mouse lemur primary visual cortex. Our data shows that despite its small size, mouse lemurs have organized orientation preference maps in the visual cortex.
Mammalian motor cortex consists of several interconnected subregions thought to play distinct roles in voluntary movements, yet their specific role in decision making and execution is not completely elucidated. Here we used transient optogenetic inactivation of the caudal forelimb area (CFA) and rostral forelimb area (RFA) in mice as they performed a directional joystick task. Based on a vibrotactile cue applied to their forepaw, mice were trained to push or pull a joystick after a delay period. We found that choice and execution are temporally segregated processes. CFA and RFA were both essential during the stimulus delivery for correct choice and during the answer period for motor execution. Fine, distal motor deficits were restricted to CFA inactivation. Surprisingly, during the delay period neither area alone, but only combined inactivation was able to affect choice. Our findings suggest transient and partially distributed neural processing of choice and execution across different subregions of the motor cortex.
Layer, cell-type and pathway-specific thalamocortical input to mouse primary somatosensory barrel cortex

Sermet B.¹, Oram T.², Yizhar O.², Petersen C.¹

Weizmann², EPFL - BMI¹

In the mouse whisker system, sensory information is relayed to the primary somatosensory barrel cortex by two major thalamic nuclei, the ventral posterior medial nucleus (VPM) and the posterior medial nucleus (POM). While the axonal innervation pattern of these two nuclei has been studied anatomically in some detail, their synaptic input to distinct cell-types across different layers in barrel cortex is incompletely understood. We used the specificity of optogenetics to selectively stimulate axons from VPM or POM, and we measured the evoked excitatory postsynaptic potentials in vitro with whole-cell patch-clamp recordings. VPM or POM was infected in vivo with an adenoassociated virus encoding the light-gated cation channel channelrhodopsin (ChR2). Synaptic input onto individual neurons of the barrel cortex was recorded in brain slices in vitro by activating the ChR2-expressing thalamic axons with blue light. We first measured thalamic inputs onto excitatory neurons across all layers of the barrel cortex, finding that the biggest inputs appeared to largely colocalise with the anatomical innervation pattern. Anatomically, VPM preferentially innervates L4, deep L3 and the L5B/6A border, and, functionally, we found that the biggest input was observed in L4, followed by L2/3. Anatomically, POM innervates L5A and L1, and, functionally, we found the biggest input in L5A, followed by L2/3. In ongoing experiments, we are measuring the input from POM and VPM across cortical layers onto three distinct classes of GABAergic neurons, expressing parvalbumin, somatostatin or vasoactive intestinal peptide. Our results begin to provide a more complete understanding of the distribution of thalamic input to specific cell-types across the layers of the mouse barrel cortex.
Lateralized trigeminal stimulations can automatically orient spatial visual attention

Ischer M.¹, Delplanque S.², Sander D. ²

Unige - FAPSE², UNIGE - Faculté des Sciences¹

Almost all perceived volatile compounds stimulate both the main olfactory system and the trigeminal system. Through the trigeminal system, it is possible to intentionally pay attention to a scent and spatially localize it, but whether a scent is capable of automatically orienting spatial attention intermodally remains unknown. Yet, i) there is a common pool of attentional resources shared across sensory modalities, ii) the trigeminal system enables humans to differentiate a stimulation delivered to the left or the right nostril, and iii) trigeminal stimulations create alert responses and can thus be considered relevant stimuli, which are particularly prone to capturing an individual’s attention. We used CO₂ and eucalyptol as lateralized cues in a variant of the visual spatial cueing paradigm in seven studies with varied delay between the cue and the target. In valid trials, cues and targets were presented on the same side, whereas in invalid trials, they were presented on opposite sides. As predicted, an intermodal effect was observed: reaction times in valid trials were faster than invalid trials. We found that the delay between the trigeminal cue and the visual target is crucial to show this effect.
Central and Spinal Effects of a Cortical Plasticity-Inducing Non-Invasive Brain Stimulation Technique

Stephan A.M.¹, Benninger D.H.¹

CHUV¹

A neural substrate for motor learning is allegedly long-term enhancement of synaptic efficacy in the primary motor cortex, generated by repetitive activation of somatosensory afferents. Recently, a transcranial magnetic stimulation (TMS) paradigm was developed to assess such plastic abilities in humans. The paired associative stimulation (PAS) technique pairs repetitively a peripheral and a motor cortical stimulation, in order to induce associative long-term potentiation and depression in the primary motor cortex (M1). As the cellular mechanism on which it is believed to rely, the effect of the intervention is timing-dependent. When TMS is timed to be delivered to M1 approximately synchronously with the arrival of the afferent signals, a facilitatory effect is induced, as demonstrated by an increase of motor evoked potentials (MEP) amplitudes. Whereas, when M1 stimulation is delivered shortly before sensory afferents arrival to the cortex, it induces an inhibition of motor excitability. This technique could represent a mean to investigate the state of cortical plasticity in neurological disorders and assess the effects of treatment and physical therapies in motor disorders. However, little is known of the extent of its effects. Here, we employed this paradigm in healthy volunteers and assessed motor excitability with single and paired-pulse TMS and spinal inhibition with paired peripheral nerve stimulation before and after intervention. We observed an increase of MEPs after PAS, whereas intracortical inhibition and spinal inhibition remained unchanged by the intervention.
Lactate is provided to neurons by transport from astrocytes. Besides the metabolic functions of lactate, the recent discovery of a G protein-coupled receptor (GPCR) for lactate in neurons of the central nervous system, called hydroxycarboxylic acid receptor 1 (HCA1R), has pointed to additional non-metabolic effects of lactate on neuronal network activity. The aim of this work was to characterize the intracellular pathway mediated by the activation of HCA1R in neurons, and to investigate the cooperation between HCA1R and other GPCRs for the modulation of neuronal network activity. The non-metabolized agonists of HCA1R, 3,5-DHBA and 3-Cl HBA, reversibly decreased the spontaneous spiking activity of primary cortical neurons of wild-type mice by 40%. Neither compounds affected the activity of neurons prepared from HCA1R knock-out animals. We observed that HCA1R in neurons mediates its effect through the inhibition of adenyl cyclase, decreasing cAMP levels and PKA activity. These results together with previously published data on the Gi protein deactivator PTX ability to reverse L-lactate effect in neurons, strongly supports the notion that HCA1R in the central nervous system is mediating its effect through a Gi protein, as was previously demonstrated in adipocytes. A characteristic feature of GPCRs is their ability to cross-talk with other GPCRs. We found that HCAR1 cooperates with the adenosine A1 receptor, GABAB receptor, and ?2-adrenergic receptor for the modulation of the neuronal network activity. Our results underlines the requirement of HCA1R activation and the non-metabolic nature of the lactate effects on neuronal activity. This study supports the idea that lactate can be considered a gliotransmitter able to modulate the neuronal activity through GPCRs.
Postsubicular glutamatergic afferents target highly focal portion of limbic thalamic reticular nucleus in mice.

Vantomme G.¹, Rovó Z.¹, Katsioudi G.¹, Lüthi A.¹

UNIL-DNF¹

The Thalamic Reticular Nucleus (TRN) is a thin GABAergic nucleus that has an inhibitory control of the dorsal thalamus across multiple temporal and spatial scales. The TRN is already known as 1) a key player in the generation and boosting of oscillatory activity 2) a cornerstone of attentional mechanisms 3) and can control the vigilance state.

Far from being a homogenous nucleus, accumulating evidence suggests considerable heterogeneity in the neurochemical nature and the synaptic connectivity of the TRN. Furthermore, its anterior portion receives limbic cortical afferents (from retrosplenial and cingulate cortex), yet little is known about its role in thalamo-cortical communication.

Investigating the organization of thalamic inhibition by the TRN, especially its anterior portion, may lead to the identification of new functions of this inhibitory nucleus wrapped around the thalamus.

We identified, by retrograde tracer labeling, a projection from the PostSubiculum (PostS) to the anterior TRN. The anterodorsal thalamus to PostS circuit is involved in the Head Direction signal, an essential component of the self-referenced navigation system. Neurons encoding for the head direction are most prominently found within these two structures. Although the TRN controls all dorsal thalamus through feedforward inhibition, its role in the head direction system remains largely unexplored and is investigated in this study.

We used anatomical and functional techniques to determine the nature of postsubicular afferents to the TRN. Anterograde tracers and AAV1-CaMKII-ChR2-YFP were injected into the PostS complex of mice followed by in vitro and in vivo electrophysiological recordings combined with optogenetic stimulation.
Experience-dependent synaptic plasticity in the lateral habenula

Trusel M.

UNIL-DBCM

In everyday life, proper behavioral responses when foreseeing an unpleasant event are necessary for survival. We hypothesized that, during the formation of an association between an external stimulus and the successive administration of a punishment, plasticity at excitatory synapses occurs in the epithalamic nucleus lateral habenula (LHb). To investigate this issue, we probed synaptic transmission onto LHb neurons from animals at different stages of learning in an active avoidance paradigm (30 trials/day, 5 days). The animals learned to avoid a footshock preannounced by a tone already from the second and third sessions (“learners”). Control mice instead received the footshocks and the CS randomly, not contingently. 24h after training session 2 we measured spontaneous excitatory postsynaptic currents (sEPSC) in acute brain slices containing the LHb. The frequency of sEPSCs, but not amplitude, was significantly increased in the LHb of learners, compared to control mice. Recording trains of EPSCs revealed similar paired-pulse ratios between learners and controls. We then measured AMPA and NMDA currents elicited by electrical stimulation within the LHb, observing a significant increase in AMPA/NMDA ratio in learners compared to controls. Furthermore, AMPA/NMDA increase also occurred when evoking EPSCs using uncaging of glutamate in the proximity of dendrites. Optogenetic stimulation of specific input fibers, from the Lateral Hypothalamus (LH) or the medial VTA (mVTA), indicated that AMPA/NMDA is increased specifically at LH- but not mVTA-to-LHb synapses. These data suggest that learning to predict an aversive stimulus engages post-synaptic strengthening at excitatory synapses in the LHb.
miR-709: a micro regulator of EEG cortical synchrony

Kompotis K.¹, Mang G.¹, Jimenez S.¹, Emmenegger Y.¹, Franken P.¹

UNIL-CIG¹

MicroRNAs, 18-25 nucleotide long non-coding RNAs, fine-tune a plethora of neuronal processes and pathologies. However, their role in sleep regulation remains understudied. We sleep deprived (SD) mice for 6h and performed a microRNA-array analysis to determine which microRNAs are affected by sleep loss. Expression of miR-709, a microRNA previously associated with epileptic models and stress, was upregulated in both cortex and hippocampus, as confirmed by in situ hybridization. The functional involvement of miR-709 in sleep homeostasis was assessed by in vivo down-regulation using miR-709 LNA inhibitors (Exiqon, Denmark). The EEG response to a 6h SD was measured in mice injected intracerebroventricularly (ICV) with either a) the miRNA-709 inhibitor, b) a non-functional “scrambled” control, or c) artificial cerebrospinal fluid (aCSF) as a vehicle control. Injection of the miR-709 inhibitor resulted in higher levels of EEG slow delta (0.75-2.25 Hz) power after periods of either spontaneous or induced wakefulness, as compared to the controls. Interestingly, top predicted miR-709 gene targets (TargetscanMouse 7.1) in cortical neurons are involved in axon guidance and synaptic processes. Moreover, miR-709 is upregulated after activation of metabotropic glutamate receptors, which are directly involved in sleep homeostasis. miR-709 might therefore functionally link neuronal excitation during extended wakefulness to the recovery process occurring during sleep.
Oxytocin receptor signaling in the prefrontal cortex modulates the inhibition of fear responses by the amygdala.

Triana Del Rio R.¹, van den Burg E.¹, Hegoburu C.¹, Scheggia D.¹, Ciobanu C.¹, Giobellina G.¹, Stoop R. ¹

CHUV¹

The projections from different areas in the medial prefrontal cortex (mPFC) to the amygdala modulate fear expression and extinction. Here, we hypothesized that the oxytocin receptor (OTR) modulates the inhibition of cells in PL that project to BLA. OTR activation (400nM) increases the frequency of spontaneous inhibitory post synaptic currents (sIPSCs) more than 30% from the baseline, in about 40% of projecting cells within the PL (L2 & L5). This effect has to be shown to be repeatable, and blocked with the specific antagonist OTA. The present results showed possible action potential-driven events (hypothetically in SST+ INs) due to OTR activation.

In ongoing experiments, the activation of OTR during extracellular stimulation seems to increase the amplitude of evoked IPSCs in projecting cells (PL). This suggests that the OTR signalling could inhibit the projections from PL to BLA.

II. Oxytocin receptor activation in PL inhibit fear retrieval, and facilitates social buffering of fear consolidation in vivo.

To test behaviorally the role of the OTR to inhibit the cortico-amygdaloid pathway of fear consolidation, this receptor was blocked with a specific antagonist (OTA) in vivo, using two different protocols that show the development of fear consolidation though the retrieval of fear memories.

1. Fear conditioning/active avoidance: During fear conditioned/ avoidance learning, in vivo inactivation of OTR in the PL increased fear expression measured as freezing behavior, while increasing the latency and decreasing the frequency of footstock active avoidance during fear retrieval. This indicates the importance of OTR signaling to modulate the different fear responses after retrieval.
A single-scan protocol for absolute D2/3 receptor quantification with [123I]IBZM SPECT

Tsartsalis S. 1, Tournier B. 2, Ginovart N. 3, Millet P. 3

UNIGE - Belle-Idée 1, Belle-Idée 2, UNIGE-Belle-Idée 3

Purpose Molecular imaging of the D2/3 receptor is widely used in neuropsychiatric research. Non-displaceable binding potential (BPND) is a very popular quantitative index, defined as the product of the receptor concentration (Bavail) and the radiotracer affinity for the receptor (1/appKd). As the appKd is influenced by parameters such as the endogenous neurotransmitter dynamics, it often constitutes a confounding factor in research studies. Here, we describe the use of a partial saturation protocol that permits to produce an in vivo Scatchard plot and thus estimate Bavail and appKd separately, through a single dynamic SPECT session.

Methods Twenty-nine male rats were used. A partial saturation protocol was applied at the region- and voxel-level and results were compared to those obtained with a multi-injection model. The partial saturation protocol was applied after an adenovirus-mediated D2 receptor striatal overexpression and in an amphetamine-induced dopamine release experiment.

Results The partial saturation experiments gave similar values as the multi-injection at the regional and voxel-level. After adenoviral-mediated D2-receptor overexpression, an increase in Bavail by approximately 18% was observed in the striatum. After amphetamine administration, a 16.93% decrease in Bavail (p<0.05) and a 39.12% increase (p<0.01) in appKd was observed.

Conclusion A partial saturation protocol permits the non-invasive and time-efficient estimation of Bavail and appKd separately. This method may be applied for the in-depth study of the dopaminergic system in translational molecular imaging studies. It can dissociate the variations in receptor density (Bavail) from affinity (1/appKd), which reflects the interactions of the receptor with its endogenous ligand.
Reconstruction of the nigrostriatal dopaminergic pathway in Parkinson’s disease, using a functionalized hydrogel scaffold

Filippova A.

UNIGE - CMU

There is a vast potential in using porous hydrogel scaffolds to study and treat human diseases. They can be functionalized as drug delivery systems or used as extracellular matrix-like support in cell replacement therapies.

Parkinson’s disease (PD) is a neurodegenerative disorder, characterized by the progressive death of dopaminergic neurons of the substantia nigra (SN). Cell replacement has the potential to provide a cure for PD. Previous trials have shown poor survival of transplanted neurons, possibly due to a hostile extracellular environment, as well as dyskinesia, possibly occurring as a result of unnatural dopaminergic stimulation from the striatal graft.

The aim of our project is to generate a transplantable dopaminergic track within a three-dimensional porous hydrogel scaffold. Chemical properties of the scaffold were adjusted to maintain consistent porosity, mechanical properties and benefit cell survival. We now evaluated several adhesion molecules to select conditions providing optimal cell attachment on the scaffold. Several neurotrophic factors and structural variations of the scaffold will be tested for stimulation of directional growth of dopaminergic axons. Electrophysiological properties and dopamine release will be used to assess the functionality of neurons and neurites, extended within the gel. Upon transplantation of the system into the SN with projections towards the striatum, the track is expected to restore a more natural dopaminergic tone, and avoid dyskinesia. Simultaneously, the incorporated neurotrophic factors may promote cell survival within the unfavourable environment.
**EEG resting-state functional connectivity predicted by structural connectivity measures**

Mullier E.¹, Griffa A.¹, Vohryzek J.¹, Knebel J.-F.², Murray M.², Michel C.³, Hagmann P. ¹

CHUV¹, UNIGE³, CIBM²

Diffusion MRI allows the reconstruction of the fibers bundles that constitute the structural connections between brain regions. Other modalities (fMRI, EEG) provide information about functional connectivity. In recent years, the relationship between brain structure and function has been studied to understand the role of structural connectivity in predicting functional connectivity. Several structural measures have turned out to be reliable partial predictors of MRI functional connectivity[1]. It remains unclear whether such results can be replicated with EEG connectivity. Here we aim to: a) study the structure-function relationship using resting-state EEG and structural predictors derived from DSI; b) classify the structural measures according to their performances in explaining functional connectivity. Structural network measures such as the Euclidean distance, number, length of streamlines, shortest paths lengths are computed from the structural networks of 10 healthy subjects to be used as structural predictors. A GLM is done according to these structural predictors to find the best model. EEG connectivity is partially explained by some of the structural predictors derived from structural connectivity. Among the selected predictors, two describe to great extent the functional connectivity: the Euclidian distance and the number of steps. Thus, a linear combination of these two predictors constitutes the best model to fit the values. EEG functional connectivity is partially explained by structural connectivity. The results confirm the crucial role of the white matter connectivity architecture in shaping functional brain activity. EEG functional connectivity can be used as an indicator of pathological alterations in brain connectivity and white matter integrity.
Neuronal signature of social novelty exploration in the VTA: implication for Autism Spectrum Disorder

Prévost-Solié C.

UNIGE - CMU

Novel stimuli attract our attention, promote exploratory behavior, and facilitate learning. Atypical habituation and aberrant novelty exploration have been related with the severity of Autism Spectrum Disorders (ASD) but the underlying neuronal circuits are unknown. Here, we report that the activity of ventral tegmental area (VTA) dopamine (DA) neurons promotes the behavioral responses to social but not object novel stimuli, supports social novelty preference, and mediates the reinforcing properties of social novel stimuli. Social novelty exploration is associated with the insertion of Calcium-permeable GluA2-lacking AMPA-type glutamate receptors at excitatory inputs onto VTA DA neurons. These novelty-dependent synaptic adaptations persist upon repeated exposure and sustain social interaction. Global or DA neuron-specific knock down of the ASD risk gene Neuroligin3 alters both social novelty exploration and the reinforcing properties of social stimuli. These behavioral deficits are accompanied by an aberrant expression of GluA2-lacking AMPA-receptors at excitatory inputs onto VTA DA neurons and an occlusion of novelty-induced synaptic plasticity. Altogether, these findings causally link an impaired novelty exploration in an ASD mouse model to VTA DA circuit dysfunction.
Coupling of pupil size fluctuations to cortical states during sleep subserves a protective function for the brain

Yuzgec O.

UNIGE - CMU

During wakefulness, pupil diameter can reflect changes in attention, vigilance and cortical states. How pupil size relates to cortical activity during sleep remains however unknown. Pupillometry during natural sleep is inherently challenging since the eyes are usually closed. Here, we present a novel head-fixed sleep paradigm in combination with infrared Back-illumination pupillometry (iBip) allowing robust tracking of pupil diameter in naturally sleeping mice. We found a tight coupling of cortical activity and pupil size during slow wave sleep and conversely, pupil size was found to be a good predictor of sleep states. Furthermore our results indicate that the oscillations of pupil during sleep are mediated via the parasympathetic system and might play a protective role for sleep continuity. These findings reveal a fundamental one-to-one relationship between cortical activity and pupil size which has so far been hidden behind closed eyelids.
Beyond Unpleasantness. Social exclusion affects the experience of pain, but not of equally-unpleasant disgust.

Antico L., Amelie Guyon, Zainab Khatun Mohamed, Corrado Corradi-Dell’Acqua

Theory of Pain Laboratory, Department of Psychology, Faculty of Psychology and Educational Sciences, University of Geneva, Geneva, Switzerland

Being excluded by our peers elicits suffering, similarly to the case of painful events. Seminal theories posit that the human brain represents social and physical suffering through partly-shared code, as suggested by evidence that social rejection affects subsequent pain reports, but also that partly similar neural substrates underlie the two kinds of experiences. However, the nature of this shared code is still debated. Social exclusion might recruit a modality-specific representation that is unique for pain, or alternatively a supra-modal code for properties common to many aversive experiences (unpleasantness, salience, etc.). To shed light on the information shared between social and physical suffering, we engaged 25 volunteers in a virtual ball-tossing game with four other individuals, two of which interacted with the participant (social inclusion), whereas the other two played only with one another (social exclusion). After each game session, participants were subjected to a painful temperature, or to a comparably-unpleasant disgusting odour. Subjective reports and physiological responses converge in showing that participants were less sensitive to painful stimuli after being excluded than when they were included in the game. This effect was neither observed for disgusting stimuli, nor for thermal/olfactory neutral controls. Importantly, the effect of social exclusion on the experience of pain was more pronounced in those subjects who felt more excluded during the task. These findings indicate that the relationship between social and physical suffering does not generalize to the case of disgust, thus suggesting a shared representational code at the level of modality-specific components of pain.
K+ clearance and glutamate uptake from the extracellular space (ECS) during neuronal activation are two of the many active roles played by astrocytes. The mechanisms underlying these specific functions are accompanied by transmembrane water movements, which challenge the astrocyte volume constancy. Cell volume homeostasis is essential for survival, especially in the brain where consequences of deregulation can be dramatic. It is likely that cell volume regulatory mechanisms are also involved in the processes of ion clearance and neurotransmitter uptake. Practically, to grasp these multifaceted astrocyte processes, we have developed a multimodal approach, combining quantitative phase digital holographic microscopy (QP-DHM), epifluorescence imaging and mathematical modeling. This approach provides the ability to quantitatively monitor both cell volume and transmembrane water movements as well as the intracellular concentrations of the specific ionic species including [Na⁺], and [K⁺], at the same time. Mathematical modeling helps us to identify the relevant mechanisms underlying astrocyte cell volume homeostasis. Preliminary results obtained from such multimodal measurements performed on primary cultures of mouse astrocytes have confirmed that: 1) Increased extracellular K⁺ levels causes astrocyte swelling through mechanisms involving the activation of sodium-potassium-chloride cotransporter NKCC1. 2) Glutamate applications of 200µM during 2 minutes induce astrocyte swelling through the activation of GLAST glutamate transporters. Furthermore, these multimodal measurements have permitted to stress that water influx are temporally offset by the GLAST-mediated [Na⁺] rise and continues after washout of glutamate, suggesting that the glutamate mediated net water influx must depend upon another mechanism that still remains to be clarified. On the other hand we can show that astrocyte cell volume regulation after glutamate application strongly depends on extracellular [K⁺]. An additional study is ongoing to evaluate the effects of Noradrenalin on astrocyte cell volume and ion homeostas.