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Stress is a major risk factor for cardiovascular diseases and stress-related disorders have been shown to correlate with cardiovascular dysfunctions. In previous studies, rats submitted to stress during puberty have been shown to be less social, more aggressive and more anxious than control animals. Additionally, subgroups of rats that were selectively bred according to their level of habituation to stress between postnatal day 28 (P28) and P30 [in term of their corticosterone (Cort) responses] displayed different behaviors: rats with the highest Cort secretion after stress were more anxious and aggressive at adulthood in comparison to the animals with the lower Cort response (habituating more to repeated stress exposure). However, little is known about the effects of stress experienced during puberty as well as the differences in stress habituation on the autonomic regulation of heart-rate. In this study, the cardiovascular function of peripubertally stressed rats and rats selected for differential Cort habituation responses to stress was recorded with fully-implanted telemetry devices at adulthood. We found that rats stressed during puberty displayed a decrease in parasympathetic regulation of basal heart-rate recorded during one week at P137-144. Similarly, a decrease in the parasympathetic component of the heart-rate was noticed during a restraint stress challenge at P148, but no differences in resting heart-rate and in response to restraint were found when rats were tested one month later (P169-192). These results indicate a transient alteration in parasympathetic regulation of heart-rate following peripubertal stress during early adulthood that is not observed at later time points.
The brain contains nutrient monitoring circuits that maintain energy homeostasis by regulating individual's behavior and metabolism. These circuits have been mainly described in the hypothalamus and the brainstem. We wondered whether similar mechanisms exist in forebrain areas, and more specifically in the cerebral cortex. We focused on the insular cortex (IC) because it plays an important role in integrating body metabolic signals and in adaptive behaviors. Neuroimaging studies and previous work from our lab has shown that it is affected by feeding states. We asked whether nutrient sensing mechanisms exist in IC that could account for its ability to monitor and regulate body energy levels. We established a transgenic activity reporter system to tag putative glucose-responsive neurons with a fluorescent protein in vitro. Using whole-cell recordings, we confirmed that fluorescently-labelled cells are glucose-sensing neurons. Their response to glucose was cell-autonomous and followed a glucose-inhibited pattern driven by the opening of 2-pore domain potassium channels. Post-recording reconstructions identified them as a homogeneous population of layer 5 pyramidal cells. In the future, we will investigate the role of those neurons in animal's physiology and behavior with cell-specific activity manipulation methods.
Electrophysiological correlates of visual binding errors after bilateral parietal damage

Pedrazzini E.

UNIGE - HUG

The most dramatic expression of binding failures in vision are illusory conjunctions (e.g. the confusion between the shape of one stimulus with the color of another stimulus). Illusory conjunctions may be observed in healthy participants when exposure is limited or during free viewing in patients with parietal damage. Previous studies have attributed illusory conjunctions to failures of spatial localization of the stimuli. However, it is unknown whether such failures reflect the impairment at the level of early or late stages of visual processing. Here, we examined the time-course of visual processing using evoked potential measures in a patient with bilateral damage to the posterior parietal cortex presenting prominent binding failures. The patient was asked to identify either one colored letter briefly flashed to the left or right hemifield, or two simultaneously presented letters. In unilateral presentation she adequately identified either the color or the shape of left or right letters. In contrast, during bilateral presentation she either showed complete extinction of the left letter or an illusory conjunction between right letter shape and left letter color. Evoked potential analyses revealed an electrophysiological signature starting ~70 ms after stimulus onset that was specific to the occurrence of an illusory conjunction. These findings indicate that illusory conjunctions reflect failures of early stages of spatial processing relying on the posterior parietal cortex.
Local versus global and retinotopic versus non-retinotopic motion processing in schizophrenia

Lauffs M.

EPFL - BMI

Schizophrenia impairs cognitive function as much as perception. For example, patients perceive global motion in random dot kinematograms less strongly, because the integration of the dots into a single Gestalt is complex. Similarly, the perception of apparent motion is impaired, because the filling in of the illusory trajectory requires complex processing.

Here, we investigated very complex motion processing using the Ternus-Pikler apparent motion display. First, we tested whether the perception of global apparent motion is impaired in schizophrenics compared to healthy controls. The task required both the grouping of multiple objects into a coherent Gestalt and the filling in of its illusory motion trajectory. Second, we tested the perception of rotation in the same stimulus, which in addition required the computation of non-retinotopic motion.

Contrary to earlier studies, patients were not impaired in either task and even tended to perform better than controls. We argue that deficient neuromodulation, rather than motion processing deficits, explains the differences observed in previous studies.
The effect of environment in reinforcement learning tasks

Xu H., Herzog M.

EPFL - BMI

Reinforcement learning is a type of supervised learning, where reward is sparse and delayed. For example in chess, a series of moves is made until a sparse reward (win, loss) is issued, which makes it impossible to evaluate the value of a single move. Still, there are powerful algorithms, which can learn from delayed and sparse feedback. In order to investigate how visual reinforcement learning is determined by the structure of the RL-problem, we designed a new paradigm, in which we presented an image and asked human observers to choose an action (pushing one out of a number of buttons). The chosen action leads to the next image until observers achieve a goal. Different learning situations are determined by the state-action matrix, so called environments.

We first tested whether humans can utilize information learned from a simple environment to solve more complex ones. Results showed no significant evidence supporting this hypothesis. We then tested this paradigm on several environments with different graph theoretical features, such as regular vs. irregular environments. We found that humans performed better in environments which contain less state-action pairs to the goal. We tested various RL-algorithms and found them to perform inferior to humans.
Effects of stress within the mother-toddler relationship on individual differences among school-age children: EEG preliminary results

Pointet V.

UNIGE - HUG

The current study is a longitudinal follow-up of the children (5 to 9 years old), who already participated at the Phase 1 of the Geneva Early Childhood Stress Project. Results obtained during Phase 1 of the GECS-Pro demonstrated disturbances in emotion regulation, in the relationship between mothers suffering from interpersonal violence-related posttraumatic stress disorder (IPV-PTSD) and their children. In the present follow-up, we expect to find that children directly exposed to violence and/or to atypical maternal behavior linked to maternal IPV-PTSD will continue to show disturbances in emotion regulation, such as greater internalizing symptoms (i.e. anxiety, depression) and/or greater externalizing behaviors (i.e. aggression, impulsivity). These disturbances in emotion regulation can also have an impact on neural activation and more specifically on attentional and emotional processing. EEG permits us to consider specific patterns of neural activation or biomarkers of these phenotypic expressions of disorder.

We recorded an EEG at rest and during an emotional face matching task in 12 subjects. The task requires matching faces that share similar emotions. In addition to the EEG recording, we also measure reaction time and accuracy of responses during the EFMT. Preliminary results showed group-specific and condition-specific modulations of amplitude of the ERP components P1, N170 and P2. In terms of behavioral findings, we showed similar results to those demonstrated in the literature during an EFMT.

This understanding of differences in cortical activity in children who were raised by mothers with IPV-PTSD versus mothers without PTSD (controls), controlling for children’s direct exposure to violence, will help us to improve intervention models for families exposed to violence and so as also to interrupt cycles of its intergenerational transmission.
Biased behavioral decisions and brain responses to food with traffic light labeling

Bielser M.-L., Knebel J.-F., Murray M., Toepel U.

CHUV - UNIL

Obesity has reached dramatic proportions over the last decades, notably due to the abundance of tempting foods partially leading to overeating and weight gain. Since the evaluation of hedonic properties of food tend to exceed homeostatic energy needs, new means to attain healthier food choices and resistance to food temptations are needed. Our study investigated the impact of traffic light cues (as used for nutritional value labelling on food packages) on behavioral and brain responses to food images. We recorded visual evoked potentials (VEPs) to color images of foods (high-fat and low-fat) and non-foods from 16 healthy, non-dieting, and normal-weight participants. Images were preceded by either ‘green’, ‘red’ or ‘off’ traffic light cues during a food/non-food categorization task. Additionally, the liking of food items was rated using a 5-point Likert scale. Categorization accuracy was decreased when high-fat foods were preceded by ‘green’ as compared to ‘off’ cues. Traffic light cues affected early stages of sensory processing of food images (i.e. 115-160ms), presumably prior to decision-related activity. Estimations of neural source activity and its modulation by traffic light labelling, as well as analyses of correlation between behavioral and brain responses will further delineate the influence of color cues on food perception and appreciation. The results will thus serve to elaborate the utility of traffic light labeling as means to guide food choices, not only in experimental settings, but, in extension, being a potential means to interfere with everyday food choices for the benefit of body weight management.
The nucleus accumbens modulates the interaction between social and physical pain in borderline personality disorder

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Social exclusion causes emotional “pain” which activates brain areas similar to physical pain. Evidence suggests social pain can cause hyper-/hypo-sensitivity to physical pain, yet exactly how they interact is poorly understood. We investigated how the perception of physical pain is modulated by preceding social pain in 21 borderline personality disorder patients (BPD) compared with 24 healthy controls (HC). BPD patients often engage in self-injurious behaviors following social exclusion to decrease feelings of social pain, suggesting a competition between both types of pain experiences. We hypothesized that this effect in BPDs implicates changes in opioid-receptor-rich brain networks. Participants played a virtual ball-tossing game (“Cyberball”), with blocks of social inclusion or exclusion followed by a painful or non-painful thermal stimulation. Cerebral activity was measured by functional MRI. BPDs differed from HCs in how they processed pain subjectively and in brain areas related to social pain processing (amygdala and temporal poles) following blocks of social exclusion, but not inclusion. Finally, BPDs showed increased nucleus accumbens (NAcc) activity, an opioid and oxytocin-receptor-rich region, for hot stimuli following blocks of exclusion (unlike HCs). We also found that activity in the NAcc was mediated by anxious-attachment style, a factor which is thought to play an important role in the etiology of BPD. Together, these findings suggest a neural mechanism whereby physical pain interacts with social pain in BPD, and may thus explain why these patients often engage in self-injurious behaviors.
**Executive functioning and Music-based training in seniors – A prevention study of fall risks.**

Fernandez N. 1, Hars M. 2, Herrmann F. 2, Vuilleumier P. 1, Trombetti A. 2

*UNIGE - Other1, UNIGE - HUG2*

Falls are common in seniors older than 65 years. Evidence suggests that executive functions (EFs) may be linked to gait stability and deficits thereof correlate with higher fall risk. Exercise interventions are known to prevent falls in elderly. The current study combines clinical and fMRI measures to determine the EFs impairment in seniors and their relationship with fall risks. Then we evaluate the corresponding impact of a training on falls, on EFs during functional tasks and changes in brain circuits.

142 seniors (mean 74 y) took part in a weekly exercise training (either a music-based multitask (JDE) or a multicomponent gym senior program (GS)). Clinical measures were collected and 34 of the seniors were scanned (before and after training) when performing a coordination task.

At baseline, the fMRI behavioral results (RTs) show that participants were slower in the dual-task condition compared to both simple conditions and reveal larger patterns of activations compared to the simple conditions. Parametric regressor analyses identify associations between regions activated during dual-task condition and clinical measures. After the training, participants were not faster to perform the tasks. Nevertheless, seniors reveal reduced activations mainly in the fronto parietal network. Further analyses indicate different effects of training between groups.

In sum, RT and brain activity show that elderly have greater difficulties to perform concurrent tasks. The association observed between stronger attention network recruitment and better clinical parameters indicate that executive decline is related to vulnerability and fall risk. Specific training program can however induce beneficial cerebral changes in seniors.
Sensory vestibular stimulation in mice and its effects on sleep

Kompotis K. 1, Perrault A. 2, Emmenegger Y1., Bayer L. 2, Schwartz S. 2, Mühlethaler M. 2, Franken P. 1

UNIL-CIG1, UNIGE-CMU2

Slow rhythmic sensory stimulation (0.25Hz), broadly known as “rocking”, facilitates the transition to sleep and increases delta (1-4Hz) and spindle (11-15Hz) activity in the sleep EEG of healthy humans. In this project we investigated whether this effect is conserved in mice, to establish a mouse model to elucidate the mechanistic aspects of the phenomenon.

C57BL/6J mice implanted with EEG/EMG electrodes were rocked in the horizontal plane at three different frequencies (0.25, 1, and 1.5Hz) during the light period. EEG/EMG signals were recorded continuously for two stationary days, one rocking day, and another stationary day, for each frequency. Shaking at 1Hz recapitulated the observations made in humans; NREM sleep was also promoted in the mouse, especially within the first three hours after the start of shaking. Rocking at 1Hz also shortened sleep onset latency after a 1h sleep deprivation. We hypothesized that the effects of rocking on sleep are mediated, at least in part, by the vestibular system. To test this hypothesis, we used the tilt mouse that has deficits in the vestibular system due to a point mutation in Otop1. Homozygous tilt mice did not show the beneficial effect of rocking on sleep quantity or sleep onset latency while the response in wild type littermates resembled that of C57BL/6J mice.

We have established a mouse model allowing us to investigate the mechanisms by which rocking impinges on the sleep circuitry. The results confirm the involvement of the vestibular system and could help develop a non-pharmacological intervention to treat sleep disorders.
Dissecting the effect of 16p11.2 gene dosage on brain structure

Martin S. ¹, Rodriguez-Herreros B. ¹, Maillard A. ¹, Modenato C. ¹, Draganski B. ¹, Jacquemont S. ²

CHU Sainte Justine², CHUV¹

Proximal 16p11.2 Copy Number Variants (CNV) are associated with cognitive deficits and Autism Spectrum Disorders. These CNVs presents either as a deletion - onesupramarginal and precentral gyri, and fronto-striatal connections. The main effects of study si copy of the genomic region or duplication - three copies. This number of genomic copies is correlated negatively with the global brain metrics, as well as regional structural changes in key areas of the reward system, language circuitry and social cognition (Maillard et al., 2015¹). Our aims were to extend these findings in a larger dataset and to identify the “pure” effect of the CNV and brain anatomy changes related to additional genetic variants. We pooled together two 16p11.2 CNV cohorts from Switzerland and the United States. We analysed structural magnetic resonance images from 74 deletions and 69 duplication carriers, 66 intrafamilial controls (individuals of the same family who do not carry a CNV), 103 extra-familial controls. Our results replicate the previously published pattern of gene dosage dependent changes extending over the bilateral insula, putamen, superior and middle temporal gyri, inferior frontal, te on brain anatomy are negligible. By comparing CNV carriers to intrafamilial controls, and the latter group to extrafamilial controls, we underline the “pure” effect of the CNV, whereas a substantial amount of the brain anatomy changes is driven by differences between extrafamilial and intrafamilial controls. These results suggest a neurodevelopmental loading in the family members and a powerful genetic additive effect in the modulation of brain structure by the 16p11.2 CNV.
A preclinical model resembling the operational definitions of DSM criteria for alcohol use disorder.

Jadhav K. ¹, Halfon O. ², Magistretti P. ³, Boutrel B. ¹

CHUV², BMI/EPFL/CNP³, CNP/CHUV¹

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: Interindividual 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.
The unfolding dynamics of vocal expression of emotions are crucial for the decoding of emotional state of an individual. In this study, we analyzed how much information is needed to decode a vocally expressed emotion (anger, disgust, fear, joy, sadness, or neutral) through onomatopoeia or affective bursts by using a gating paradigm. The stimuli, onomatopoeias (e.g.: "aah"), representing each emotion were divided into increasingly longer gates from 50ms to full duration. Participants (n=80) rated the emotional content of the stimuli presented in a pseudorandom order at different gates. Each participant only judged a fraction of the stimuli (105) since the data set contained a total of 8400 utterances. Using Generalized Linear Mixed Model (GLMM), we showed that the emotions were mostly recognized above chance, some (fear, anger, and disgust) more than others (joy, sadness, neutral). Recognition improved over time with different respective function shapes (e.g. linear, quadratic) depending on the emotion presented. Acoustic features were extracted for each stimulus and a Principal Component Analysis was computed for each emotion. The best principal component was successfully used to partially predict the accuracy of recognition. These results support the importance of studying the time course of the conscious recognition of vocal emotions from emotional prosody, and reveal important variations among emotions. It is likely that these effects are due to the relevance of threatening information to the brain and related urgent motor responses when people are exposed to clear or potential threats, compared to emotions where no such urgent response is required (e.g. happiness).
Do changes in resting-state EEG predict spatial working memory decline during aging?

Klencklen G., Jabes A., Banta Lavenex P., Brandner C., Lavenex P.

UNIL-other

Spatial working memory performance declines particularly in about 50% of individuals during normal aging. Interestingly, spontaneous theta activity has been shown to decrease with age, and predict verbal working memory performance in adults. Here, we tested the possible link between changes in resting-state brain activity and allocentric spatial working memory decline during aging. We recorded eyes-closed resting-state EEG in old and younger adults, and tested their real-world allocentric spatial memory performance. We hypothesized that the power of theta might correlate with spatial working memory performance. If this hypothesis is validated, spontaneous brain activity may be used to predict spatial working memory performance and serve as an additional biomarker for screening for memory decline in normal aging and neurodegenerative disorders.
Cortisol Suppression During Sleep Enhances Memory Re-consolidation in Humans

Antypa D. 1, Rimmele U. 2

UNIGE - Other1, UNIGE2

Recent evidence shows that human episodic memory can undergo changes after reactivation through a process called reconsolidation (for review: Schiller & Phelps, 2011; Nadel et al., 2012; Agren, 2014; Forcato et al., 2014). Alterations of glucocorticoid levels may be one way of manipulating reconsolidation processes (Coccoz et al., 2011, 2013; Akirav and Maroun, 2012; Dongaonkar et al., 2013; Drexler et al., 2015). Previous human studies point towards the possibility that the cortisol synthesis inhibitor metyrapone may alter not only retrieval, but possibly also reconsolidation processes (Rimmele et al. 2010, 2015; Marin et al. 2011). In a double-blind, within-subject, counterbalanced design each participant learned two stories in a first session. Two days later, participants were given a reminder cue for one of the stories together with metyrapone vs. placebo. The reactivation was followed by three hours of sleep. Memory for both stories was tested four days later with a recognition test, after manipulation effects and re-consolidation processes should be completed. After a washout period of one week, participants underwent the condition they had not been tested before. Reactivated stories followed by cortisol suppression under sleep were remembered better than re-activated stories followed by normal cortisol levels under sleep (main effect of medication: F (1, 18) =5.486, p=.031), while memory performance for the non-reactivated stories did not differ between the metyrapone and placebo condition (medication x re-activation interaction: F (1, 18) = 6.035, p = 0.024). These findings suggest that cortisol suppression during sleep can enhance reconsolidation of memories in humans.
Comparison of different estimators for time-varying directed connectivity using benchmark EEG data

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To investigate dynamic directed interactions between brain regions from EEG or LFP signals a number of Granger-causal methods have been developed. These methods are often based on time-varying multivariate autoregressive (tvMVAR) modeling. Here we test how well different tvMVAR-based methods recover the directed connectivity in real data where the ground truth is known. We used benchmark epicranial EEG data recorded in rats after single whisker stimulation to systematically compare the performance according to fixed criteria, defined as ability to: i) detect contralateral primary sensory cortex (cS1) as the main driver of the cortical network; ii) identify peak-driving from cS1 at plausible latencies; iii) correctly distinguish the main targets of cS1. We compared performance for two alternative Kalman filter approaches: 1) estimating tvMVAR models for single trials and then average model estimates across trials (AA-approach), and 2) fitting one model to all trials using a General Linear Kalman Filter (GLKF). Furthermore, we addressed the effects on performance of revised definitions of the partial directed coherence (PDC), an MVAR-based measure of directed interactions, comparing different normalizations and evaluating the effect of spectral weighting. On criterion i), AA-approach always achieved good performance, while GLKF gave good results only with a specific normalization or applying spectral-weighting. On criterion ii), better temporal dynamics were found for the GLKF-approach. Good performances were obtained on criterion iii) for all evaluated approaches. Overall, the results showed consistently good performance of the AA-approach, whereas the GLFK approach sometimes failed to detect the major cortical driver.
Infra-slow fluctuations in neural and cardiac activity mark periods of continuity and fragility in mammalian species

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Mammalian sleep has to meet two opposing needs: a continuity for its beneficial effects on brain and body, and a fragility towards sensory input and threatening stimuli. We assessed arousability in naturally sleeping mice through repeated noise exposure and found periods of increased and decreased responsiveness, orchestrated in a 40-45 seconds cycle. Specifically, the phase of a 0.02 Hz-oscillation in the sleep spindle band (10-15 Hz) and in the heart rate predicted arousals or sleep through the noise. Oscillations were found throughout sensory and associative cortices. Acoustic evoked potentials, recorded in deep cortical layers of the auditory cortex, are modulated in waveform depending on the 0.02 Hz-oscillation phase, corroborating the hypothesis that stimulus-driven awakenings occur in well-defined temporal windows. Moreover, periods of sleep continuity were accompanied by enhanced hippocampal ripple activity, possibly favoring offline memory processing. Zolpidem, a widely used hypnotic, suppresses the 0.02-Hz oscillations, substantiating their role as markers for sleep fragility. We also investigated variations in autonomic output as possible sources for the 0.02 Hz-oscillations. Blocking sympathetic nerve activity through atenolol reduced heart rate, yet kept 0.02 Hz-oscillations in EEG sigma power unaltered. Additionally, this 0.02 Hz-oscillation is also a feature of human non-rapid-eye-movement (non-REM) sleep and this conjoint presence points to an evolutionarily conserved function of mammalian sleep and offers a novel variable to describe sleep fragility, also in conditions of disturbed sleep. Here we show that continuity and fragility are balanced on a previously unrecognized time scale that is invariant across non-REM sleep in mammalian species.
Endogenous beta-band processes reflect readout and comprehension of time-compressed speech

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Recent psychophysics data suggest that speech perception is not limited by the capacity of the auditory system to encode acoustic information by neural gamma activity, but rather by the time given to the brain to decode it. Whether the decoding process is bounded by the capacity of theta rhythm to follow speech syllabic rhythm, or constrained by a more endogenous top-down mechanism, e.g. involving beta activity, is unknown. We addressed the dynamics of auditory decoding in speech comprehension, by challenging independently the syllable tracking and speech decoding processes using intelligible and non-intelligible time compressed auditory sentences. We measured EEG in human participants and found that neural activity in both theta and gamma ranges was sensitive to syllable duration. The phase of theta rhythm followed linearly the syllabic rate without significant change in power, even when this rate went beyond the classical theta range. The power of low-gamma activity increased linearly with syllable duration (1/syllable rate), whereas the power of low-beta activity decreased only when intelligibility dropped. Consistent with their role in stimulus driven (bottom-up) versus endogenous (top-down) mechanisms, we found different dynamics for low-gamma and low-beta activity, with a build-up of beta activity with more contextual information. These data show that speech comprehension is constrained by the interplay between stimulus-driven theta and low-gamma activity and endogenous low-beta activity, but not by the capacity of theta activity to passively follow the syllabic rhythm.
Towards a resolution of conflicting models of illusory contour processing in humans 2.0: lines, orientation, and laterality

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CHUV

Illusory contours (ICs) refer to the perception of borders in the absence of contrast gradients. Despite decades of research on the psychophysics and neurobiological mechanisms of IC processes across a multitude of species and using a range of brain imaging/mapping techniques, debate continues as to whether or not ICs are the result of a low-level (presumably feedforward) process or instead occur first in higher-order brain regions. Studies supporting a low-level mechanism have most often involved stimuli inducing IC lines rather than IC forms/shapes. By contrast, studies in humans have most often involved IC forms/shapes and identified a visual evoked potential (VEP) correlate of IC sensitivity, the “IC effect” that onsets at ~90ms and is localized to bilateral lateral occipital cortices (LOC). This IC effect is observed across a wide range of stimulus parameters, though always involving object forms. The IC effect is moreover delayed in time (i.e. ~200ms onset) and has a lateralized topography/localization when the stimuli are presented to one or the other visual hemifield. The present VEP study addressed this knowledge gap by presenting IC stimuli that induce perceptions of lines that were oriented horizontally or vertically and were also presented centrally or laterally (left/right) within the parafovea (i.e. 5°). IC sensitivity to induced lines modulated the VEP topography at ~250-300ms and seems reflect retinotopic visual field representations. These results are consistent with effects originating within low-level visual cortices, albeit at relatively late stimulus processing stages. We conclude by situating these results within existing modelling of IC processing.
Gene-environment model for psychosis: Evaluation of long-term effects on behavior.

Schnider M.

CHUV

Psychiatric disorders are caused by an interplay between different genetic as well as environmental risk factors. Psychosocial stress during in adolescence has been shown to increase the prevalence of psychiatric disorder like schizophrenia. Further, reduced levels of glutathione, the main intracellular antioxidant, has been found in SZ patients. In the present study we investigated the effect of stress at two different timepoints during the development in a mouse model for redox dysregulation (GCLM KO mice). We found that stress between P30-40 lead to anxiety like behavior in elevated plus maze and open field in adulthood without affecting hippocampus or prefrontal cortex dependent behavior. In contrast, the same stress applied between P50-60 induces hyperlocomotor activity and problems in reversal learning without changing the anxiety like behavior. This indicates that depending on the timing of stress different brain areas are affected leading to a different pattern of symptoms in adulthood.
Perceiving emotional expressions in others – a series of activation likelihood estimation (ALE) meta-analyses

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Every day we consistently discriminate, identify, and evaluate other people’s emotions. In other words, we make decisions about which emotions we perceive. We conducted a series of activation likelihood estimation (ALE) meta-analyses to determine the commonalities and distinctions between separate levels of emotion perception, namely incidental processing, passive observation, and explicit evaluation of emotional expressions. Pooling together more than 180 neuroimaging experiments using facial, vocal or body expressions, our results are threefold. First, explicitly evaluating the emotions of others recruits brain regions associated with the sensory processing of expressions, such as the occipital face area, fusiform face area and the superior temporal gyrus, and brain regions involved in low-level and high-level mindreading, namely the posterior superior temporal sulcus, the inferior frontal cortex and dorsomedial frontal cortex. Second, we show that only the sensory regions were also consistently active during the passive perception of emotional expressions. Third, we show that the brain regions involved in mindreading were active during the explicit evaluation of both facial and vocal expressions. We discuss these results in light of the existing literature and we conclude by proposing a cognitive model for perceiving and evaluating the emotions of others.
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 as lateralized cues in a variant of the visual spatial cueing paradigm in four 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 this effect varied as a function of the delay between the trigeminal cue and the visual target.
Inter-individual variability in metacognitive ability for visuomotor performance and underlying brain structures

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Metacognition refers to the ability to discriminate between one's own correct and incorrect decisions. The neurobiological underpinnings of metacognition have mainly been studied in perceptual decision-making. Here we investigated whether differences in brain structure predict individual variability in metacognitive sensitivity for visuomotor performance. Participants had to draw straight trajectories toward visual targets, which could unpredictably deviate around detection threshold, report such deviations when detected, and rate their confidence level for such reports. Structural brain MRI analyses revealed that larger gray-matter volume (GMV) in the left middle occipital gyrus, left medial parietal cortex, and right postcentral gyrus predicted higher deviation detection sensitivity. By contrast, larger GMV in the right prefrontal cortex but also right anterior insula and right fusiform gyrus predicted higher metacognitive sensitivity. These results extend past research by linking metacognitive sensitivity for visuomotor behavior to brain areas involved in action agency (insula), executive control (prefrontal cortex) and vision (fusiform).
Peripheral administration of Lactate produces antidepressant-like effects

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Emerging evidence supports a role for L-lactate as an intercellular signaling molecule involved in synaptic plasticity. Many studies have shown that major depression and chronic stress are associated with alterations in structural and functional plasticity. These findings led us to investigate the role of L-lactate as a potential novel antidepressant.

In this study, we show that peripheral administration of L-lactate produces 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 concentrations and by changes in phosphorylation levels of GSK3α/β and CREB as well as in mRNA levels of Arc, COX-2 and NOS1. Further investigation revealed that chronic administration of L-lactate induces antidepressant-like effects in two animal models of depression that respond to chronic antidepressant treatment including the open-space forced swim test and the corticosterone model of depression. In particular, chronic administration of L-lactate partially restores mobility in the open-space forced swim test and completely reverses the corticosterone-induced anhedonia-like behavior. Characterization of the mechanisms involved in the chronic antidepressant-like effects of L-lactate has revealed that these effects are accompanied by changes in the expression of target genes implicated in serotonin receptor trafficking, astrocyte functions, neurogenesis, NO synthesis and cAMP signaling.

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.
Neurodegenerative Loss of Amygdala Inhibition and Hyper Anxiety: A comparative analysis of MCI and Urbach Wiethe Disease

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This project examines hyper-anxiety in mild cognitive impairment (MCI) patients. Emotional symptoms, including anxiety, are frequent in MCI and present a major difficulty for both patients and caregivers, but they remain poorly understood.

This project focuses on the role of the basolateral and central amygdala (BLA and CeA) in these symptoms, as the amygdala is known to be a critical region for anxiety, and amygdala atrophy is a common early neurological sign of MCI and Alzheimer’s disease (AD) patients. The CeA is important for the instinctive fear response, whereas the BLA is thought to exert modulatory control over CeA function. Recent evidence suggest that the amygdala damage in MCI and AD is limited to the BLA.

In order to assess the amygdala’s role in MCI-related anxiety we are concurrently working with a population of very rare Urbach Wiethe Disease (UWD) patients who have damage specific to the BLA bilaterally, while detailed fMRI has shown preserved function in the CeA. Hyper-anxiety has been demonstrated in these subjects, likely arising from a loss of inhibitory control through the BLA over the CeA. We hypothesise that hyper-anxiety in MCI may arise in a similar manner.

In order to investigate this hypothesis we are examining anxiety in MCI and UWD patients by means of a variety of experimental affective neuroscience tasks. Finally, the results will be correlated with various psychological and neuropeptide characteristics of the participants, in order to assess which patients are most at risk of developing anxiety symptoms.
The effects of action video-games on the processing of attended and unattended emotional stimuli

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Previous studies have shown that playing action video games can lead to improvement in attentional control. However, all these studies have used exclusively non-emotional stimuli. Thus, the aim of the present study is to determine whether the attentional control would also be improved in the case of emotional stimuli, such as faces expressing emotions.

To address this question, action video game players (AVGPs) and non-action video game players (NVGPs) performed an attention-demanding task in which they were presented with two streams of faces flickering at different frequencies, and were asked to focus on one stream only to detect specific emotions (e.g. happiness or surprise presented along anger or disgust), while ignoring the stream on the other side. To measure the neural response subtending the attention allocated to the attended as well as to the ignored streams of stimuli, we recorded EEG and extracted steady-state visual evoked potentials (SSVEPs) elicited by the two sequences of flickering stimuli.

Based on the existing literature, our analyses focus on testing (i) at the behavioral level, whether AVGPs perform better than NVGPs in terms of accuracy or reaction time; (ii) at the neural level, whether AVGPs show greater suppression of the unattended distracting stream of faces to a greater extent than NVGPs, or (iii) whether they may be showing an enhanced response to the to-be-attended stream. Alternatively, we may find no difference between groups, which would suggest a rather specific enhancement of attentional control in AVGPs that does not extend to emotional stimuli.
Abstract # 27

Fine spatial-frequency structure of EEG alpha rhythm in healthy humans

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CHUV

Waking alpha rhythms (AR, 7–13 Hz) consist of several oscillatory components characterized by different scalp distribution and reactivity to sensory stimulation and movement. Collectively, the variants include central mu rhythm, temporal tau rhythm, anterior AR, and the most widespread and powerful posterior AR. The latter is either considered as a unitary rhythm, or is subdivided into 2 or 3 AR components (ARC). This division is based on frequency-specific AR correlates to visual stimulation, memory and attention tasks, and other indirect findings. In this study, we aim to extract ARC in individual subjects based on their frequency, spatial and temporal features. For doing so, we recorded high-density EEG of thirty young healthy subjects (20-45 years old). Each recording session was 2-2.5 hours consisted of several tasks intermingled with resting periods. Our analysis was based on the 10-s EEG segments that allow the high frequency resolution of 0.1 Hz and provide a reliable estimation of the fine structure of AR in individual subjects. The methods included source spectral analysis followed by the AR decomposition by means of Parallel Factor Analysis (PARAFAC). In this group, we found that majority of the subjects (90%) had an individually stable AR structure including 2-3 occipito-parietal and occipito-temporal ARC. In the next step of this project, we will study the structure of ARC in aged subjects (45-70 years old) as well as mild cognitive impaired subjects. We expect that detailed knowledge of AR structure will be useful for monitoring age-related and neurodegenerative processes in the human brain.
Effects of Atomoxetine on executive functioning and functional brain imaging in adolescents with attention deficit disorder with or without hyperactivity

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Background and objectives:
Children with attention deficit disorder with or without hyperactivity (ADHD) present difficulties in executive functions, specifically working memory (WM) (Willcutt et al., 2005).
Evidences suggest potential benefits of atomoxetine (ATO) treatment that may extend beyond reduction of core ADHD symptoms to amelioration of some neuropsychological and functional deficits.
A trial was performed on 17 adolescents suffering from ADHD and compared them with a control group of 15, age, sex and socio-economic status matched controls. Using functional brain imaging (fMRI) and a behavioural task, we will study the effects of (ATO) in a prolonged administration (12 weeks) on executive functioning.
Methods:
A functional magnetic resonance imaging (on a 3T) was conducted with 18 participants with ADHD and medication and 14 healthy controls. The assessment was carried on once before any medication (T1) and a second time after the drug treatment (T2).
During the scans, the visuo-spatial task consists in remember the red points presentation and then to reproduce with a joystick.

Results and Conclusion:
Activation start bilaterally in high order visual areas extending to parietal regions involved in multisensory integration and visual-spatial processing. Such neuronal substrates are known as encoding and retrieval of WM abilities.
The comparison after treatment revealed that ATO treatment did not allow to normalize WM abilities, but a decreased activation, for the retrieval, of the right inferior frontal gyrus after ATO treatment for ADHD. This study showed a more efficient brain functioning after ATO treatment, which is not related to better WM abilities.
Improvement of real-time fMRI for clinical applications

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Real-time fMRI neurofeedback is an emerging imaging technique that allows the subject to gain voluntary control over a target brain region. Previous results show that self-regulation of brain activity is feasible and may have beneficial effects on targeted disorders. However, as the field is in its infancy, there are several conceptual and methodological issues that are currently unresolved.

During my PhD work I tried to address some of these issues including the following questions:
• How is neurofeedback mediated in the brain?
• How does the choice of target area influence neurofeedback?
• How do personality or habits impact neurofeedback success?
• Does feedback timing affect neurofeedback outcome?

Here, I will mainly focus on the latter question comparing two different feedback timings in a clinical population (tinnitus patients). We compared between continuously presented feedback and intermittent feedback that is presented after the self-regulation period.

To this aim, 14 subjects with subjective, continuous tinnitus received either continuous (n=7, n(female)=1, age: 46.77 +/- 12.01, initial TFI score: 49.42 +/- 15.07) or intermittent (n=7, n(female)=2, age: 47.36 +/- 12.39, initial TFI score: 49.82 +/- 20.28) feedback of their auditory cortex. All subjects underwent a total of 9 down-regulation runs over 3 sessions.

Neuroimaging results indicate that the continuous group outperformed the intermittent group in auditory cortex down-regulation. Behavioural results are non-significant but on a descriptive level the continuous group tends to show slightly better outcomes.

In conclusion, continuous neurofeedback seems to be superior to intermittent feedback in a clinical population when looking at a sensory target area.
Resting EEG microstates changes after acute exercise

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Multichannel electroencephalography (EEG) recording during relaxed wakefulness is a promising neuroimaging technique to investigate spontaneous brain activity changes after exercise. EEG microstates analyses showed that the majority of signal can be explained by only four stable microstates (Lehmann et al., 2009). The temporal characteristics of the microstates have a neurophysiological relevance in humans. Thus, this study aims to identify the effect of physical exercises on microstates temporal features.

Twenty triathletes performed two successive exercises on a cycle ergometer. Before (PRE), between (POST1) and after (POST2) the two sessions, spontaneous resting EEG was recorded during 3 minutes. EEG datasets were submitted to a k-means clustering to identify the 4 dominant microstates and conventional microstates parameter were computed (mean duration, relative time coverage and frequency of occurrence).

The analyses revealed that the four cluster map solutions explain above 84% of the global topographic variance. ANOVAs indicated significant Time by Map interactions for the mean duration (F(6,114)=7.5, p<0.001) and the relative time coverage (F(6,114)=7.4, p<0.001) of map C only. Bonferroni post-hoc tests revealed that both variables increase at POST1 and POST2 compared to PRE. No significant effects were obtained for the frequency of occurrence.

Microstates C was previously shown to correspond to a specific network with main generators in the anterior cingulate and the insula cortices (Britz et al., 2010). These results are in line with the literature as these regions are involved in the integration of sensory feedback and emotional information. Thus, post-exercise microstate C changes could reflect the exercise-related afferent activity.
The role of Somatostatin–expressing GABA neurons of the Medial amygdala in aggressive behavior in mice

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EPFL - BMI

The medial amygdala (MeA) integrates sensory pheromonal information and relays it to various brain areas, including the hypothalamus, lateral septum and extended amygdala. Neurons in the MeA have been implicated in control of innate social behaviors such as aggression, sociability and social memory, which are often affected in psychiatric disorders. However, the precise neural circuit mechanisms underlying these behaviors are not known. Therefore, we would like to understand the wiring and the function of distinct neuron populations in the MeA, by using in vivo and in vitro optogenetic approaches. Cre-driven mouse lines are used to target specific neuron types. We observed that optogenetic stimulation of somatostatin-positive (SOM+) neurons in the posterior part of the MeA inhibit aggressive behavior in resident-intruder test. We also find using Cre-dependent tracing virus and histological reconstruction, that SOM+ neurons are long-range inhibitory projection neurons and that they target nuclei in hypothalamus, lateral septum and bed nucleus of stria terminalis. In vitro optogenetic stimulation of the SOM+ terminals in their hypothalamic target nuclei confirmed certain functional connectivity. In summary, our preliminary data show that SOM+ neurons may play a role in suppressing ongoing aggression, possibly via inhibiting hypothalamic target neurons. These findings provide an important ground for the future behavioural studies aiming on characterization of the posterior MeA inhibitory circuits involved in social behaviours.
Peripersonal space and body representation in virtual reality: a pilot study

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EPFL - BMI

How PPS and BR of the hand are modulated in virtual reality has been poorly investigated. Here, we tested if PPS and BR representations of the hand are modulated by the observation of a virtual hand displaced towards subjects’ midline. Before and after observation, 16 healthy subjects performed two tasks to evaluate PPS and BR, respectively.

In the first task, we evaluate hand BR by asking participants to move a cursor on a bar to indicate the perceived position of their right index finger, while wearing an HMD.

In the second task, we evaluate PPS representations by instructing subjects to respond to tactile stimuli delivered on their right index finger while they were ignoring a ball moving in vertical plan and arriving to two different positions, one corresponding to the perceived real hand position and one corresponding to the position of the displaced virtual hand.

We found that after observation, the perceived position of the right index finger significantly shift toward the body midline. Moreover, while at baseline participants were faster to answer to tactile stimuli when associated to the moving ball near the real rather than virtual position, this facilitatory effect disappear after the observation of the virtual hand.

Together, these findings demonstrate that mere observation of a virtual hand displaced towards the midline affects both PPS and BR representation of participants’ real hand, suggesting a visual capture effect. This result supports the possibility to use PPS and BR tasks to assess embodiment in virtual reality.
Optimal delineation of motor somatotopy in cortical and subcortical regions using fMRI

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CHUV¹, UCL²

The accurate delineation of motor somatotopy is crucial to better understand movement disorders. Previous fMRI studies on motor somatotopy in deep brain nuclei used different spatial resolutions and reported various levels of overlap between different body parts. In this study we compared the ability of various fMRI protocols at different resolutions (1.5mm, 2mm and 3mm isotropic) to discriminate more or less segregated motor somatotopy patterns in cortical and subcortical areas. In order to quantify the segregation between activations of different body parts, we calculated an index of functional specificity (FSI), which is a weighted average angle between subject-level beta estimates at each voxel per region of interest. Results of the ANCOVA revealed that the effect of spatial resolution on FSI varies across brain structures. Additionally, post-hoc tests revealed that brain regions with overlapping patterns of motor somatotopy, such as BG, thalamus and SMA are sensitive to the effect of spatial resolution, whereas motor somatotopy representations in M1 do not benefit from a higher resolution. We discovered that 1.5mm EPI globally yields higher FSI values. Moreover, 2mm EPI provided higher BOLD signal strength as compared to the other EPI protocols. We demonstrate that brain regions associated with fine-grained somatotopy patterns benefit from a gain in resolution as compared to cerebral structures associated with highly segregated patterns at baseline. Our method provides an objective and automated framework that may help to optimize future fMRI acquisition schemes or to investigate how functional segregation can be affected by diverse pathological conditions.
The hemispheric dominance for auditory and visual spatial representations in the inferior parietal lobule reversed by prismatic adaptation.

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CHUV

Prismatic adaptation (PA) is a procedure using prisms that shift the visual input allowing alleviating unilateral spatial neglect deficits. In a previous study we demonstrated that in healthy subjects the left hemisphere, and in particular the inferior parietal lobule (IPL), is subserving the changes in spatial visual field representations following PA. The aim of the present study was to investigate if the functional modulations induced by PA are specific to the visual modality or if the same pattern of modulations would be found during an auditory detection task. To that end we designed a within-subject event-related fMRI experiment. Sixteen healthy subjects (8 males, mean = 28yo) underwent fMRI acquisitions during a visual and an auditory detection tasks before and after three minutes of pointing movements while wearing 10 degrees rightward deviating prisms.

fMRI data confirmed that the left IPL is modulated by PA during the visual detection task but more importantly they revealed that PA modulates in a similar way the activation in the left IPL during the auditory detection task. During both tasks, the ipsilateral (i.e. left) field representation is increased in the left IPL. Activation in the cerebellum, superior temporal gyrus and hippocampus were also observed in all conditions. In conclusion, PA modulates the left parietal activation similarly during the detection of auditory and visual targets. Our study suggests that this low-level intervention is modulating high-order brain areas involved in multimodal spatial representations. PA reverses the well known right hemispheric dominance for auditory localization.
The Influence of Transient Affective States on Attention Tasks

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UNIGE - FAPSE

Theoretical Background:
- Lasting effects of transient affective stimuli on Intrinsic functional networks (Ifn’s)
- Variability in Resting state Networks undergoing Transient Affective stimuli
- Impact of cognitive load on Ifn’s. Task-activated brain regions (red) recover slower after task performance.

Aims:
- Observing the influence of the negative emotional episodes on attention task and subsequent resting-state activity
- Observing the Recovery of IFNs activity over time
- Differentiating the IFNs modulation according negative-valence stimuli.

Hypothesis
- Congruence Sequence Effect and/or Congruence Effect is larger following the negative stimuli than neutral condition.
- Neural underpinnings: Cognitive control (ventral ACC, dorsal ACC) is significantly sensitive to emotional content.
- Neg.emotion stimuli influence the temporal dynamics of Ifcn’s following the attention task: Timescale of recovery and different temporal patterns (variability and stability)

Methods:
- One fMRI scanning session per participant. Duration: 80 minutes.
- Population: 30 Healthy female subjects. Right handed. Without psychiatric or neurological disorder.
- Emotion induction: Sadness and Neutral. videoclips
- Physiological recordings (Heart rate, respiration, pupil dilation
- Attention task: Flanker and stroop tasks. 1 Block per condition (80 trials per block)

Behavioral Results:
Congruence Effect:
- Reaction time (RT) is faster in congruent trials than in incongruent. In both neutral and sad condition
- RT decreased in sad condition

fMRI Results:
- Analysis of fMRI data is on process.
Internally driven sensorimotor synchronization: a behavioral study

Barbosa C., Geiser E.

CHUV

Sensory motor synchronization to a rhythm is observed when people play music or dance. No expertise is required; humans are able to spontaneously synchronize body movements to auditory rhythms. Tapping in synchrony with an auditory cue involves temporal synchronization between sensory (external cue) and motor (body movement). To determine if synchronization is possible without a combination of motor and sensory temporal alignment we used a finger tapping task where the tapping phase is preceded by a passive listening to a regular auditory sequence phase (purely sensory cueing). We aim to establish if tapping synchrony to a regular rhythm can be accurately perpetuated in absence of auditory stimulation. Consequently, a synchronization (auditory input), a continuation (in silence) and a passive listening condition were compared in the tapping phase. Subjects tapped the tempo of he previously listened auditory sequence once the entraining phase stopped. 3 tempi were used to test the influence of tempo on the tapping accuracy and precision. Across conditions and tempi subjects tapped accurately to the sound sequence. 195 tempo performance accuracy was higher than slower tempi, plus subjects were more accurate in synchronization condition. Two behavioral patterns were observed: a predictive pattern during synchronization, with subjects tapping ahead the tempo, and a reactive pattern during continuation, in which they tapped behind of the tempo. Conclusively, purely sensory cued tapping is accurate even when stimulation ceases, indicating that purely sensory cueing is enough to induce an internally driven state that perpetuates in time, allowing people to tap with the tempo.
Neural correlates of reality filtering in psychosis

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UNIE- HUG4, HUG - SPG3, UNIGE - HUG1, UNIGE -HUG5, UNIGE- HUG2

Psychosis is characterized with symptoms of hallucinations and delusions, which reflect a difficulty to distinguishing things not pertaining to reality. Orbito-frontal (OFC) lesions also may induce a confusion of reality, as evidenced by patients acting upon their confabulations and by disorientation. These patients typically failed at a continuous recognition task to indicate picture repetition within an ongoing run rather than across identical runs. The mechanism normally repressing the interference of memories from previous runs is “orbitofrontal reality filtering” (ORFi) and is characterized in healthy subjects with a distinct positive frontal potential at 200-300 ms.

Here we explored whether reality confusion in psychosis was also characterized with disturbed ORFi. We recorded high-density electroencephalography from patients diagnosed with psychosis, matched with healthy controls, at rest and while performing two runs of our task.

The level of hallucinations correlated with the number of false positives in the second run. Successful processing induced a positive frontal potential at 250-300 ms in both groups. Inverse solutions localized this activity, which was stronger in patients, to the OFC. Patients and healthy control then also displayed additional differences at a later timing. Resting state connectivity also differed between groups. Patients had higher alpha coherence in right primary auditory and insular area, but lower gamma coherence in OFC. Both measures were inversely correlated with levels of hallucination.

These findings suggest that patients with psychosis may generate the early OFC signal associated with ORFi in healthy subjects but that subsequent stimulus processing is abnormal. These processing differences may reflect differences in underlying resting-state connectivity.
Gentle rocking boosts deep sleep and declarative memory

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Why do we cradle babies or irresistibly fall asleep in a hammock? Based on our previous nap study (Bayer et al., 2011; Current Biology), we aimed at assessing the effects of slow rocking on whole-night sleep and its possible effect on overnight memory consolidation using polysomnography on healthy adults. Therefore, eighteen participants from 20 to 27 years old spent two experimental nights in a custom-made bed, which either remained in a stationary position or rocked gently at 0.25Hz. To assess memory retention, participants performed a word-pair associate learning task before and after sleep in both conditions.

EEG data revealed that rocking shortened sleep latency to sleep stage N2 (p=0.043) and increased the time spent in deeper sleep stage N3 (p=0.001). Analyses of NREM EEG oscillatory activities revealed that rocking (compared to the stationary condition) increased spindle density during N3 (p=0.003) and reduced arousal density during NREM, in particular N3 (p=0.023). Memory data analysis showed a significant effect of rocking on overnight improvement in the number of word-pairs recalled (p<0.028), especially for words with a negative valence (p<0.05). A positive correlation was found between the difference (rocked - stationary) of density of fast spindle during N3 and the difference of memory accuracy on paired-words with a negative valence (r²=0.343; p=0.017).

The present results suggest that rocking yielded a faster building up and a better maintenance of deep sleep. Also, these new findings show that a continuous low-frequency rhythmic stimulation may boost deep sleep and memory processes occurring during sleep.
Can we improve motor recovery by inhibiting the contralesional motor cortex in the first weeks after stroke? A randomized controlled trial

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Introduction: Non-invasive brain stimulation (NIBS) is promising for enhancing recovery after stroke. Yet, the effects vary and the impact on plasticity is unclear. In this study, we aim to compare the effect of two inhibitory NIBS techniques on markers of brain plasticity and motor recovery in stroke.

Methods: We performed a study including standardized motor assessments, high-density electroencephalography (EEG), and diffusion tensor imaging (DTI) on 41 patients with hemispheric stroke. Patients were assessed before (T0) and after (T1) protocol.

Results: At T1, patients treated with tDCS showed greater beta-band functional connectivity between the ipsilesional motor nodes (M1) and rest of the brain compared with sham ($t_{24}=2.8$, $p=.01$) and cTBS ($t_{26}=1.8$, $p=.07$). In addition, in well-recovered patients, NIBS has no influence on the degradation in white matter. In contrast, cTBS and sham stimulation groups showed more decrease than tDCS patients ($p<.05$) in patients with poor recovery. Despite these changes, NIBS had no significant added effect on the recovery as compared to sham stimulation at the group level. However, in patients in whom therapy could be started within 4.5 weeks after stroke, beta-band coherence was correlated with improved recovery ($r=.70$, $p=.0038$). In this subgroup, patients treated with NIBS exhibited larger clinical effect size compared with sham (tDCS>sham Hedges’g=1.02 and cTBS>sham Hedges’g=.46).

Conclusions: These findings suggest that NIBS have complex aftereffects on network. tDCS shows beneficial modulations on structural and functional markers of motor plasticity but needs to be start at within 4.5 weeks after stroke.
Grey and white matter myelination trajectories of the human lifespan

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Aims: This is the first study to investigate quantitative MT variation across the lifespan in human grey and white matter (GM/WM). It has been established that local processes of myelin accumulation and degradation proceed at differing rates across the brain. These trajectories can be severely disrupted in disease, thus a detailed characterization of WM tissue property changes is crucial for understanding brain maturation/degradation processes and the diagnosis of abnormalities in patient groups.

Methods: 521 healthy subjects (263 -females) between the ages of 7 and 83 were scanned on a 3T Siemens Prisma MRI system. Diffusion and quantitative-MRI data were collected for each subject and diffusion-tractography used to derive structural connectivity matrices. Quantitative measures of magnetization transfer (MT) were used as a sensitive biomarker for myelination. MT maps were sampled across the cortical GM and subcortical WM pathways. A second order polynomial model was used to capture the inverted U-shape myelination trajectories. Simple measures can be extracted from the model such as age of peak maturation, peak MT value, gain in development and loss in decline.

Results: Significant Age² effects (p<0.05 FWE-corrected) were found across the human grey and white matter. GM myelination peaks later than the underlying WM (45-75yrs vs. 29-45yrs), shows a different pattern of development and changes less over the lifespan.

Conclusions: This study shows for the first time the concurrent and divergent patterns of GM and WM myelination across the human lifespan in a large cohort of 521 subjects. Such a characterization of development and normal aging provides a useful benchmark for future clinical and scientific questions related to abnormal patterns of myelination.
A data-driven model of quantification disease severity in sporadic Alzheimer's disease

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The atrophy patterns detected by MR scans correlate with neurofibrillary tangles, one pathologic hallmark of Alzheimer’s disease (AD). We propose to extract a latent variable based on atrophy pattern to quantify the disease severity for each subject by applying factor analysis. We aim to test whether the estimated severity significantly associates with clinical diagnosis at baseline and risk of clinical conversion in follow-up. We downloaded ADNI and three city study (3C) T1-weighted MR scans and preprocessed them with SPM12. ADNI includes 322 cognitive normals (CN), 693 mild cognitive impairments (MCI) and 252 AD; 3C 1447 CN. The 114 grey matter regions were segmented based on neuromorphometrics atlas and the volumes were calculated. We applied factor analysis to estimate the disease severity using regional volumes. We compared the estimated disease severity distributions between 3 clinical groups of ADNI pairs-wisely by using two sample T test. We built proportional hazards models, adjusted for age, gender, APOE ε4 and years of education for testing clinical conversion. Three clinical groups have significant different estimated severity (all p<2.2e-16). Disease severity significantly associates with clinical conversion: from CN to MCI in ADNI (hazard ratio=1.61, 95%CI 1.1 to 2.3, p=0.009), to clinical AD in 3C (hazard ratio=1.59, 95%CI 1.1 to 2.2,p=0.007); from MCI to clinical AD in ADNI (hazard ratio=1.75, 95%CI 1.5 to 2, p=2.32e-14).

Our results showed evidence that the estimated disease severity based on atrophy pattern significantly associate with clinical diagnosis at baseline and clinical conversion in the follow-up, suggesting a surrogate for quantifying disease staging in clinical practice.
Emotional regulation revealed by iEEG

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To discover where and when emotional regulation influences emotional appraisal in the human brain is of crucial importance to develop new therapeutic approaches for clinical practice. We report here the Local Field Potential (LFP) activity of 6 epileptic patients with depth electrodes undergoing an emotional regulation task. Patients had to suppress, distance themselves from, or not to regulate their emotional appraisal while rating emotional and neutral pictures presented on screen. First, LFP analysis revealed distinct amygdala (n=7) responses to the different emotional categories. Second, we found that emotional regulation strategy influences emotional appraisal in the amygdala. Indeed, we observe that emotional regulation modulates amygdala’s processing of visual stimuli, this modulation occurred between ~ 150 and 170ms post-stimulus onset. To our knowledge, this is the earliest modulatory effect of emotional regulation described so far on amygdala responses.
Effects of training modalities on learning transfer following motor inhibitory training

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UNIL-ISSUL

Although recent studies demonstrated that inhibitory control (IC) can be improved by training, how this training transfers to other executive functions and whether the complexity of training modulates this generalization remain unresolved. Using the Trail making test, the Switching, the Flanker, the Simon tasks (far transfer) and the Go/NoGo task (near transfer), we investigated the generalization of 50 minutes IC training modifications in healthy participants (n=24) by comparing the effects of simple versus complex Go/NoGo practice whose complexity is to combined several cognitive processes. By enhancing the task difficulty, one could hypothesize that the practice of complex tasks involving an IC component would modify fundamental IC performance and the underlying brain networks (currently analyzing but not presented here). As performance score, we assessed the reaction time and the percentage of false alarms at the beginning versus at the end of the 50 min IC training. Behaviorally, the complex group improved inhibitory performance by reducing reaction time while no change has been found in the simple group. In terms of generalization, we demonstrated that the task complexity was a key condition for the near transfer in the Go/NoGo generalization task. Our preliminary results sustain previous findings showing that complex Go/NoGo training leads to inhibitory control improvement. Moreover, by demonstrating that the complexity of training brings positive outcome in terms of near transfer, we showed that the domain-general IC network can be strengthened and even transfers to untrained tasks. To go further, we are currently working on the generalization of long-term Go/NoGo practice (10 hours).
Computational Neuroscience

In silico voltage sensitive dye imaging in a digital reconstruction of somatosensory cortex.

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We report on an in silico implementation of voltage sensitive dye imaging (VSDI) for exploring and validating mesoscopic neural activity in a biologically detailed digital reconstruction of rat somatosensory cortex. The cortical model comprised a network of \~775,000 neurons arranged in a five by five hexagonal grid of connected functional microcircuit units, spanning a patch of simulated tissue 1990 µm x 1840 µm in area and 2000 µm deep. Two methods of acquiring in silico fluorescence signals were compared for computational performance, namely Monte Carlo simulation and a Beer-Lambert law-based approximation of light scattering and absorption in tissue. We evaluated the behavior of our in silico VSDI model against several findings reported in the literature, including sublinear summation of paired stimulation, activity spread velocity, and state-dependent stimulus response. Furthermore, leveraging the flexibility of our digital model, we addressed two unresolved questions concerning the origins of the VSD signal: 1) the relative importance of spiking activity vs. subthreshold fluctuations in membrane potential, and 2) the respective contributions of excitatory and inhibitory cells.
A layered approximation to the neuronal input-output relation reveals dendritic subunits

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It is widely accepted that dendritic arborizations augment the computational capacity of neurons. In particular, synaptic inputs are thought to sum non-linearly when arriving closely together, both through the voltage dependence of the driving force as well as through the non-linear magnesium block in the N-methyl-D-aspartate (NMDA) channel. This local summation has been shown to have important consequences on action potential output generation as well as local synaptic plasticity. Consequently, to understand the computation that individual nerve cells perform, it is of vital importance to understand the input-output relation that is induced by these non-linear dynamics.

In this work we present a new, 'layered' solution method that expresses the neuronal output as an explicit function of its inputs. Hence, questions about how conductance inputs in dendrites interact with each other, that have been hard to answer conclusively with simulations, can be answered immediately. We will treat in particular how inhibition interacts with excitation and examine the location dependence of subtractive and shunting influences. Related, we will also assess how the high conductance state influences compartmentalization. Finally, we will explore the conditions required for different locales on a dendritic arborization to be considered independent subunits.
Humans can learn and generate temporal dependencies that span a wide range of time scales. The longest are even several orders of magnitude higher than neural time scale. Here we investigate how artificial intelligence and recent improvement in machine learning can be used to learn the structure of such complex sequences with an application to music composition.

We present a statistical model of the behavioural decisions that composers perform when they choose to combine particular notes or rhythm. Our model employs a separation of fundamental features and multi-layer networks of gated recurrent units. Networks composed of gated recurrent units have been shown to be efficient in learning complex sequential activations with long-range dependencies. We separate the information contained in monophonic melodies into their rhythm and melody features. The model processes these features in parallel while modelling the relation between them, effectively splitting the joint distribution over note duration and pitch into conditional probabilities.

Using such an approach, we were able to automatically learn the temporal dependencies inherent of large corpora of Irish folk songs. We could use the extracted structural rules to generate interesting complete melodies or suggest possible continuations of melody fragments that are coherent with the characteristics of the fragments themselves.
Contextual effects on the neural encoding of speech sounds

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Our rich and constantly changing auditory environment requires a flexible and dynamic auditory processing system. Animal studies have shown that context can differentially influence the neural processing of frequency content. It is unknown however, how these findings translate to humans, and importantly, how they translate to naturalistic contexts. We conducted a 7 Tesla fMRI experiment in which participants performed either a linguistic or paralinguistic task on the very same speech sounds. With the use of computational modeling, we mimicked the filtering of sounds by the cochlea, as well as acoustic sound decomposition within the auditory cortex. This allowed us to model, in various brain regions, task-specific auditory response profiles, along specific acoustic dimensions, i.e. frequency, spectral modulation and temporal modulation. We found that performance of the two tasks evoked differential neural encoding of the very same sounds. During the linguistic task peak sensitivity is found for frequencies between 0.3-0.7 kHz, whereas during the paralinguistic task additional peak sensitivity is found for frequencies between 1.1 – 1.6 kHz, in different auditory areas. Interestingly, peak sensitivity for temporal modulations is found in the left hemisphere during the linguistic task, but in the right hemisphere during the paralinguistic task. These findings are consistent with findings showing that temporal modulations are important for speech processing, as well as with findings showing leftward lateralization for speech-specific processing versus rightward lateralization for voice processing. It remains to be explored whether other acoustic models that focus on different task-relevant acoustical features can better explain the auditory response profiles.
Cortical oscillations are involved in speech recognition. A recent neuro-computational model from our laboratory establishes that coupled theta and gamma neural oscillators can segment speech into syllable units and organize gamma range spiking into a decipherable neural code [1]. This model, however, lacks the notion of top-down control, which is determinant in on-line speech recognition, presumably through beta oscillations. Here we set out to understand how theta, beta and gamma oscillations interact in speech processing. We address this question at the theoretical level, using a predictive coding model of auditory cortical operations involving a hierarchy of timescales. We split stimulus content and timing processing into different model levels. In the timing level the theta oscillator tracks the syllabic rhythm through the envelope of the input signal, and organizes the activity of the timing units. These units are connected to the content level, enabling the decoding of the spectral content of the incoming stimuli. Compared to the model presented in [1], the current model was designed in a predictive coding manner. Thus, in addition to emulating implicit theta and gamma rhythms for bottom-up information flow, it also includes top-down predictive information. The present model still lacks the notion that top-down modulation preferentially uses the beta frequency channel, which observed experimentally. Our next step will hence consist in introducing such a top-down modulation to explore how it interacts with the implicit theta and gamma rhythms.

The brain on bistable illusions

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Introduction: Bistable illusions offer an opportunity to investigate perceptual decision making under uncertainty. While the brain resolves ambiguous visual stimuli, it does so in part by accommodating uncertainty with a perceptual switch. Because the perceptual switch is experienced as a discrete event, the neural processes underlying the perceptual decision can be investigated using fMRI.

Aim: We undertook to examine the neural correlates of perceptual decision-making under uncertainty using a bistable illusion (the Necker Cube) as stimulus and fMRI as a measure of neural activation. The ambiguity of the Necker Cube was manipulated parametrically by warping the cube’s angles so as to bias perception towards one view or another (from above or from below).

Method: Participants performed two tasks during fMRI acquisition. In the first task, a subject specific psychometric curve was obtained to determine individual points of subjective equality; that is the cube that elicited a 50/50 chance of being viewed from above or from below. In the second task, subjects were asked to report their first percept, as well as any subsequent perceptual switches while viewing five versions of the cube, one at a time for 80 seconds each.

Results: The variance of subjective scores from task 1 for each cube (a measure of uncertainty) was reflected in insular cortex activation, an area that is also implicated in cognitive (financial) uncertainty. In Task 2, BOLD activity related to the perceptual switch arose in the locus coeruleus as well as cingulate and insula cortex. These finding suggest that regions related to the noradrenergic system mediate uncertainty signaling across sensory domains.
Focal epilepsy leads to the emergence of a large-scale epileptic network that sustains the pathological state

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In focal epilepsy, pathological activity from the epileptic focus alters distant neuronal networks. However, how this pathological behavior spreads in the brain and how it is expressed electrophysiologically is poorly known. We aimed to study the development of large-scale epileptic networks and characterize the pathological activities emerging in the hubs of the network.

We used surface, high-density EEG combined with multiple-site intracortical recordings and video-based monitoring in the unilateral kainate mouse-model of temporal lobe epilepsy. Animals were recorded prior and after (J7, J14 and J28) induction of hippocampal epilepsy. At 7 and 28 days after kainate injection, we silenced the EF through tetrodotoxin (TTX) injection. Detection of fast-ripples (FRs) was achieved with an automatic detector.

We identify a large-scale EN, comprising both hippocampi and neocortical regions, through which numerous interictal generalized spikes (GS) propagate. We show for the first time that FRs are not restricted to the EF, but appear in regions of propagation of the EN. FRs increase significantly during the disease and do not always appear with a concurrent epileptic activity in the EF, suggesting that target regions of the EN have become autonomously pathological. To confirm this we silenced, in the chronic stage of the disease, the EF through TTX-injection: despite a complete abolition of focal spikes and seizures, we continue to observe FRs in remote brain regions, as well as GS. The same procedure done earlier showed a significant decrease of GS, indicating that at this stage, the network is dependent on the integrity of the EF.

The epileptic activity propagating from the EF leads progressively to the development of an EN with pathological activities, notably FRs, in remote brain regions. This EN becomes eventually independent from the EF.
Mitochondria and energy metabolism in Retinal Ganglion Cell differentiation

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Energy metabolism has emerged as a key parameter during differentiation and cell fate specification. Indeed, proliferating cells rely mainly on glycolysis for energy production, while adult cells use oxidative phosphorylation. Some recent studies have shown that cellular energy metabolism can directly influence cell fate. However, very little is known about the relationship existing between neurogenesis and energy metabolism. Understanding how neurons production is coordinated with metabolic switch in order to meet the new requirements of neuronal fate is of particular importance to fully comprehend the complex process of neurogenesis.

We took advantage of the chick embryonic retina, an easily accessible tissue that is part of the central nervous system, to look at the role of mitochondria in Retinal Ganglion Cell (RGC) differentiation. RGC is the first cell type to differentiate and require huge amount of ATP for proper function, making it a particularly suitable model to study energy metabolism.

We describe the distribution and dynamics of mitochondria during the time course of RGC differentiation, showing a strong apical accumulation that directly precedes neurogenesis. We characterize mitochondria redistribution during cell migration and axogenesis. More importantly, we discovered a strong increase of mitochondria that occurs in committed RGC that up-regulate Atoh7, a bHLH transcription factor that coordinate cell cycle exit and RGC differentiation. We show that Atoh7, as well as some other neurogenic bHLH can induce mitochondria accumulation. Finally, we try to identify Atoh7 targets that are responsible for the induction of mitochondria biogenesis.
Investigating the role of microRNA 137 on cortical projection neuron development

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A variety of microRNAs are expressed during cortical development and are thought to regulate early steps in the generation of cortical neurons such as proliferation and migration. 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. Based on these results, we aimed 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 over-expressed in progenitors of PNs and it’s impact on cell cycle dynamics and migration was analyzed at several subsequent embryonic time-points. Preliminary results indicate that cell cycle is shortened by miR137 overexpression and that PNs reach the cortical plate prematurely. Current studies are designed to determine the molecular mechanisms through which miR-137 controls distinct steps in the development of cortical PNs.
Wnt-related neuronal migration delay is sufficient to cause deficient cortical circuitry accompanied by autistic-like behavior

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Precisely coordinated cell migration events are crucial for neocortical development and migration errors can lead to neurodevelopmental disorders that have been implicated in psychiatric and neurological pathologies. While it has been speculated that altered neuronal migration might lead to circuit impairment, the causal evidence for this is still lacking. Previously we have found that canonical Wnt signaling regulates migration and the timing of positioning of late-generated pyramidal neurons. In order to explore how altered layer 2/3 callosal projection neuron migration impacts on the subsequent formation of cortical circuits, we transiently down-regulated Wnt canonical signaling during radial migration. We found that an isolated delay in the migration and positioning of layer 2/3 neurons of the somatosensory cortex can have long-term detrimental consequences on cortical circuit formation, sensory functions and social behavior. We observed a reduced arborization of transcallosal axons in the homotypic contralateral cortex. Using multichannel intracortical recordings of somatosensory evoked potentials, we confirmed a significantly weaker interhemispheric connectivity in animals with a delayed migration. Remarkably, late arrived layer 2/3 neurons displayed reduced activity and their pharmacological depolarization was sufficient to rescue the observed defect in callosal projections. These results demonstrate that migration errors due to transient dysregulation of Wnt signaling during radial migration can lead to abnormal connectivity of excitatory neocortical neurons, thereby potentially underlying neurological and psychiatric disorders.
Role of interneuronal KCC2 in cortical microcircuit formation

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Cortical microarchitecture is the fine result of highly dynamic network connectivity between neuronal populations. Their activity establishes the so-called excitation-inhibition balance (E/I), critical for neuronal network stability and function. The neuron-specific K+/Cl- cotransporter KCC2 plays a main role in driving GABAA receptor-mediated synaptic inhibition in the mature cortex, by tuning intracellular chloride concentration. Recent data indicate that KCC2 might also be expressed in distinct brain regions at earlier developmental stages and could play a morphological role during circuit formation. The goal of my project is to characterize the electrophysiological properties of early-expressing KCC2 cells and how they impact on the local circuitry E/I balance. Histological analyses at different early developmental time-points show that KCC2 mRNA and protein are already expressed in interneurons invading the forming neocortex. To further investigate the role of KCC2 in INs, we selectively knock-down this co-transporter in GAD65-expressing cells. Analyses of GAD65-KCC2 cortices show a significantly decreased expression of the calcium-binding protein parvalbumin (PV) and density of PV-expressing cells consistently remains lower than in controls towards adulthood. Furthermore, PV+ cells in GAD65-KCC2 mice fail to be enwrapped into perineuronal nets, suggesting impairments in the plasticity process. In parallel, morphological analyses on principal neurons (PNs) suggest an altered E/I ratio. At P30, PNs in GAD65-KCC2 animals display a decreased dendritic spine density, as well as an increase of filopodia-like protrusions when compared to controls. Electrophysiological studies will be performed to further analyze the E/I balance and altered INs properties.
Canonical Wnt signalling regulates dendritic arbor development of retrosplenial cortex neurons

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Neuronal circuits in the retrosplenial cortex (RSC) have been implicated in “resting brain state” activity, spatial memory as well as retrieval of autobiographical memory. RSC dysfunction has been linked to neurodevelopmental disorders including fragile X syndrome, autism spectrum disorder and schizophrenia. While much has been learned about the structure and functions of this cortical area, little is known about its development. Here we investigated the dendritic morphogenesis of pyramidal cells that form typical dendritic bundles in layer I of RSC. Using the TOPdGFP transcriptional reporter of Wnt/beta-catenin canonical signalling, we found that these neurons exhibit an increased GFP fluorescence once they are positioned and start dendritic development. Transient downregulation of Wnt canonical signalling during the early postnatal period leads to a significant decrease in dendritic branching that is irreversible and persists until adulthood. We identified neurotrophin-3 (NT3) as a downstream target of Wnt pathway and rescued dendritic defects by overexpressing NT3. At later time points, during critical periods of synaptogenesis, Wnt signalling is not necessary for maintaining normal dendritic arborization, however Wnt loss-of-function results in decreased spine density. Enhanced neuronal activity can rescue this effect. We conclude that canonical Wnt signalling through transcription-dependent effects is required for early dendritic development and contribute to the regulation of subsequent spine formation during critical periods of early postnatal development.
A Role for Erythropoietin Signaling in radial migration of cortical neurons

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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 largely unknown. Here we found that knockdown of EPOR in migrating late generated spiny stellate progenitors by overexpressing small-hairpin RNA expression resulted in striking changes in cell distribution pattern in the cortical plate, which persisted after the end of migration period. We observed a large number of shEPOR cells accumulated 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 as well as a decreased number of cells entering into the transition zone. Together, these preliminary observations give support to the hypothesis that appropriate activity of intrinsic EPO signaling is required for the radial migration of cortical spiny stellate neurons.
Evolution of novel glomerular targeting specificities in drosophila olfactory sensory neurons

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How novel neural circuits emerge during evolution is an important but poorly understood process. To gain insights into this question we are studying the Drosophila olfactory circuits that express 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 olfactory sensory neuron (OSN) populations that project their axons to diverent, but adjacent, glomeruli. To identify molecules involved in IR75a, IR75b and IR75c neuron axon targeting, we have pursued three complementary approaches: high-throughput gene expression analysis of developing and mature antennal tissue by RNASeq, targeted DamID (TaDa) to identify transcriptionally active genes in each OSN population, and manual isolation and transcriptomic analysis of GFP-labeled OSNs expressing diverent receptor genes.
**Interaction between Redox dysregulation and Neuroinflammation during early development could lead to PVI circuitry impairments in adulthood: relevance for schizophrenia**

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Schizophrenia (SZ) is a major psychiatric disease which involves both genetic and environmental factors. The redox system was shown to be affected in SZ, with decreased Glutathione (GSH), a main cellular antioxidant and redox regulator, observed in CSF of patient and polymorphisms in the key GSH synthesizing genes associated with the disease. Moreover, increased neuroinflammation has been reported in SZ. The interaction between both processes occurring at critical period during brain development may affect neurons vulnerable to elevated oxidative insults, such as parvalbumin-expressing interneurons (PVI) and their perineuronal net (PNN), which circuit is impaired in SZ.

We used a transgenic mouse model with GSH deficit (GCLM -/-) that shows SZ related phenotype, to investigate this interaction in early development, with an additional oxidative insult from postnatal days P10-20.

An additional oxidative insult in young mice led to decreased PVI+ and PV-PNN+-IR, increased oxidative stress and microglia activation in adult GCLM-/- . Microglia activation was more pronounced at peripubertal stage compared to adulthood, suggesting a stage-specific vulnerability. We explored the role of RAGE, which is activated by ligands produced by oxidative stress, and found increased RAGE shedding as well as increased MMP9-IR in GCLM-/- at P40. Interestingly, a specific inhibitor of MMP9 prevented RAGE shedding and microglia activation in P40 GCLM-/-, suggesting that this treatment could also limit oxidative stress and PVI/PNN deficit.

We propose that an interaction between redox dysregulation and pro-inflammatory condition via RAGE/MMP9 in early development is a potential trigger of structural and morphological impairments in adult.
Investigating the role of Dgcr2 on cortical projection neuron development

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UNIGE - HUG

Alterations in early steps of cortical circuit formation are thought to play an important role in vulnerability to schizophrenia (SZ). DiGeorge Critical Region 2 (Dgcr2) is located in the 22q11.2 locus, whose deletion is one of the highest known risk factors for SZ, and codes for an activity-dependent trans-membrane protein expressed during cortical development. In addition, exome sequencing revealed a de novo Dgcr2 missense mutation in an idiopathic schizophrenic patient. The present study intends to understand the function of Dgcr2 in pyramidal neurons migration and in cortical circuit formation. Here we investigated the expression and function of Dgcr2 in early steps of cortical circuit formation using in utero electroporation targeted to projection neurons (PNs). Knock-down (kd) of the expression of mouse (m)Dgcr2 during corticogenesis affected the laminar positioning of PNs in a persistent manner in the somatosensory cortex and the medial prefrontal cortex. PN mispositioning due to Dgcr2 kd could be fully rescued by overexpressing the human (h)DGCR2 but not the (h)DGCR2 containing the SZ-risk mutation, indicating a deleterious impact of this SZ-risk mutation on PNs migration. In order to further understand the biological function of Dgcr2, we are currently investigating the role of specific DGCR2 subdomains and studying potential binding partners. This study will bring novel insights on the role of the SZ-risk gene Dgcr2 on cortical circuit assembly.
Molecular and Cellular Neuroscience

In The Pursuit Of The Fear Engram: Identification of neuronal circuits underlying the treatment of anxiety disorder

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EPFL - BMI

Fear and other anxiety disorders are extraordinarily robust and difficult to treat. Among the most effective treatments for anxiety disorders are exposure-based therapies, during which a patient is repeatedly confronted with the originally fear-eliciting stimulus in a safe environment so that the once fearful stimulus can be newly interpreted as neutral or safe. A fundamental element for successful exposure-based therapies is the reactivation/recall of the traumatic memory, which initiates a time-limited process called memory reconsolidation, during which a memory becomes susceptible to disruption.

Presently, the neuronal subpopulations underlying successful fear memory extinction remain completely unknown, which represents a big gap in memory research. Therefore, we aim to identify these neuronal subpopulations that are causally implicated in effective attenuation of remote fear memories in order to determine whether the original traumatic memory trace has been permanently modified or a new memory trace of safety has been superimposed over the original one. Using exposure-based therapy in transgenic mice, which allows for a time-limited activation of neurons upon remote memory recall, making it not only possible to visualize those neurons but also to experimentally isolate them from the rest of the neurons for further molecular investigations.
The role of hippocampal microcircuits in memory allocation

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UNIGE - CMU1

Memory starts with the integration of information from the external world that is transformed into patterned synaptic signals and integrated at cellular and network levels in the brain. The hippocampus plays a major role in the formation and storage of declarative memories. Contextual fear memory formation drives an increase in synaptic activity in the hippocampus that recruits only a fraction of neurons in the network. Recent studies have shown that reactivation of this active ensemble is sufficient to recall the associated memory. However, the mechanisms that determine how this ensemble is formed remain elusive. The main aim of this project is to investigate the role of inhibitory and excitatory circuits in defining memory allocation in the hippocampus. What limits the fraction of neurons involved in encoding a particular memory? Do alterations in the size of active ensemble have an impact on memory persistence? We artificially manipulated granule cells activity in the dentate gyrus during memory formation. We found that neurons become part of the memory ensemble by engaging microcircuits formed by somatostatin interneurons that inhibit the dendrites of surrounding excitatory neurons. This lateral inhibition modulates the size of the active ensemble and the strength of the associated memory. Our results suggest that memory is assigned to neurons according to their level of activity and that of adjacent cells at the time of encoding. Active granule cells engage somatostatin positive interneurons that confine the size of the ensemble and control the stability of the memory over time.
Are the sleep-wake driven changes in PER2 actuated by temperature?

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UNIL-CIG

Sleep-wake rhythms are orchestrated by the interaction of a homeostatic and a circadian process. We demonstrated that one of the core circadian clock genes, PER2, also plays a key role in sleep homeostasis (Curie et al., 2015 SLEEP). However, how PER2 behaves during spontaneous waking, NREM and REM sleep, has not been studied yet due to lack of appropriate methodology. This has been overcome with a device that can measure gene expression in a freely behaving mouse (Saini et al., 2013 Genes Dev) along with EEG recordings. Our results show that PER2 is increasing during spontaneous waking, and decreasing during spontaneous sleeping. We could reliable predict PER2 levels based on the sleep-wake distribution, thereby recognizing the importance of the sleep-wake distribution in PER2 expression.

In a follow-up study, we aim to unravel the mechanism underlying this observation. Temperature is mainly sleep-wake driven, and the expression of cold-inducible RNA binding protein (CIRBP) is in turn temperature driven and therefore strongly dependent on sleep-wake history. Moreover, CIRBP is necessary for high-amplitude clock gene expression. Therefore, we hypothesize that CIRBP contributes to the sleep deprivation (SD) induced changes in PER2. We expect that mice lacking CIRBP show an attenuated response to SD in per2 expression. First data from our CIRBP KO mice shows higher delta-power after SD, indicating a faster increase of sleep need during wakefulness. Next experiments will show if per2’s increase upon SD is indeed attenuated in CIRBP KO mice. Taken together, our findings underscore the importance of sleep need in the expression of the circadian core clock genes. We are currently investigating temperature and CIRBP as a possible mechanism explaining these observations.
Abstract # 63

Defining mitochondrial biomarkers using magnetic resonance spectroscopy at 14.1 Tesla in a mouse model of mood disorders

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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 (Chaturvedi & Flint Beal 2013). Defining and following 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). (Breuillaud et al. 2009, Breuillaud et al. 2012).

Metabolic and volumetric profile alterations were determined with MRI together with 1H-MRS of prefrontal cortex (PFC) and dorsal hippocampus. Results indicated an age-dependent alteration of glutamate and GABA levels in Crtc1 KO mice PFC together with a constant reduction in phosphocreatine in the dorsal hippocampus. 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. Mitochondrial quantification using mtDNA copy number revealed a reduction of mitochondrial mass in the dentate gyrus, which could explain the observed energetic dysfunction. Together, these results suggest that CRTC1 might be an essential regulator of brain energy metabolism in the mouse dorsal hippocampus. Further investigations will aim at clarifying the mitochondrial failure of these mice and monitor its evolution with its associated MRI/MRS profile.
In vitro generation of HCRT and MCH expressing neurons from mouse fibroblasts

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UNIL-CIG

The sleep disorder narcolepsy is characterized by excessive daytime sleepiness, sleep attacks, cataplexy, hypnagogic hallucinations, and sleep paralysis. While the loss of the HCRT neurons is well established in the narcoleptic patients, the MCH neurons intermingled with HCRT neurons in the region remain totally intact. In the present project taking advantage of induced pluripotent stem cell techniques we aimed at producing neurons expressing lateral hypothalamic markers including MCH and HCRT to test their physiological properties in-vitro.

The iPS cells were established and were characterized. Coaxing iPSC lines toward hypothalamic progenitors resulted in expression of hypothalamic genes Rax, Six3, and Vax1. We observed the expression of lhx9 indicating that we have generated cells of the region lateral to PVN and VMH nuclei. Treatment of the EBs with molecules from BMP families resulted in the strong suppression of the pax2 and increased expression of six1 gene. This treatment resulted to expression of mch gene while the hcrt gene was unresponsive to that. Improving culture condition resulted to the generation of MCH neurons as verified by immune-staining of MCH and MAP2 peptides. Screening several small molecules and growth factors showed some candidates including vitamins for induction of hcrt gene expression that under verification. Experiments are ongoing to achieve bona fide MCH and HCRT expressing neurons to evaluate their transcriptional and physiological properties. Primary result shows that progenitors for HCRT and MCH cells display different responses to the same molecules.
The importance of dendritic mitochondria in the pathophysiology of 22q11 deletion syndrome

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Maugeri Foundation - UNIPV2, UNIL-DNF1

One of the strongest known risk factor for schizophrenia is the 22q11 deletion syndrome (DS), a syndrome characterized by cognitive deficits associated to structural abnormalities in dendrites formation. Six of the main candidate risk genes for behavioral phenotypes of animal model of 22q11DS (LgDel mice) [Merscher et al., Cell, 2001] encode mitochondrial proteins. Here, we examined mitochondrial gene expression using mRNA extracted from fresh tissues of LgDel mice. Our analysis showed that among others, downregulation of Bcl2 was particularly pronounced. The role of Bcl2, which encodes for mitochondrial BCL-2, in the pathophysiology of 22q11DS has never been investigated. Interestingly, a potential role for BCL-2 in the mechanisms regulating dendritic formation and maturation has been recently suggested, indicating that mitochondria not only provide dynamic energy support for normal synaptic functioning but also directly modulate synaptic structure and functional plasticity. Thus, in order to understand whether the decreased levels of BCL-2 could have a role in the neuroanatomical abnormalities associated to 22q11DS, LgDel mice have been chronically treated during the first 3 weeks of postnatal development with a biologically active peptide consisting of a domain of BCL-XL fused to the protein transduction domain of the human immunodeficiency virus (HIV) TAT protein or vehicle. Preliminary results have indicated that normalizing BCL-2 levels during the postnatal maturation of the brain circuits was sufficient to prevent dendritic abnormalities and to restore the number of dendritic spines.

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VTA projection neurons releasing GABA and glutamate in the dentate gyrus

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UNIGE - CMU

Both dopamine and non-dopamine neurons from the VTA project to a variety of brain regions. Here we examine non-dopaminergic neurons in the mouse VTA that send long-range projections to the hippocampus. Using a combination of retrograde tracers, optogenetic tools, and electrophysiological recordings, we show that VTA GABAergic axons make synaptic contacts in the granule cell layer of the dentate gyrus, where we can elicit small postsynaptic currents (PSCs). Surprisingly, the currents displayed a partial sensitivity to both bicuculline and NBQX, suggesting that these meso-hippocampal neurons co-release both GABA and glutamate. Finally, we show that this projection is functional in vivo and its stimulation reduces granule cell-firing rates under anesthesia. Altogether, the present results describe a novel connection between GABA and glutamate co-releasing cells of the VTA and the dentate gyrus. This connection could be relevant for a variety of functions, including reward-related memory and neurogenesis.
Neurological or Psychiatric Conditions

ApoE4 modulates the cortical thickness networks attributes in Mild Cognitive Impairment converters to Alzheimer disease

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CHUV

The apolipoprotein E4 allele (ApoE4) is a strong risk factor for developing Alzheimer’s disease (AD). Recent studies provide evidence to support the existence of aberrant brain connectivity in large-scale networks in AD and Mild Cognitive Impairment (MCI) (Tijms et al., 2013). However, how these changes are related to this genetic risk remains unknown. In the present work we characterized the impact of ApoE4 on the brain cortical thickness network attributes (CTNA) in MCI. To carry out our study we used 200 MCI structural Magnetic Resonance Images (sMRI) (ADNI database). Following a progression diagnostic the MCI subjects were subdivided in 100 converters (MCI-C) to AD and 100 non-converters (MCI-NC) (50 ApoE4 “carriers” and 50 “non-carriers”). The mean cortical thickness in a set of 148 structures was obtained from sMRI using FreeSurfer software. The CTNA in carriers and non-carriers were studied using the graph theory framework. The clustering index (Cp), characteristic path length (Lp) and efficiency (E) attributes were compared between groups. Our results revealed stable brain network attributes across time for MCI-NC (higher Cp, Lp, local E and lower global E in noncarriers compared to carriers). Instead, MCI-C carriers exhibited a different pattern between time points: an increase in Cp, Lp, local E and a decrease in global E for carriers. In the present study we have shown an early APOE4 modulation of the cortical thickness networks attributes in MCI. These changes seem to be meaningful in term of clinical progression.
Altered triple network connectivity is related to impaired executive functions in patients with 22q11.2 deletion syndrome: a multimodal study

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UNIGE - Other¹

Large-scale brain networks play a prominent role in cognitive abilities and their activity is impaired in psychiatric disorders, such as schizophrenia. Patients with 22q11.2 deletion syndrome (22q11DS) have an ultra-high risk to develop schizophrenia and present similar cognitive impairments, including executive functions deficits. Thus, 22q11DS represents a model for the study of neural biomarkers associated with schizophrenia. In this study, we investigated structural and functional connectivity within and between the Default Mode (DMN), the Central Executive (CEN) and the Saliency network (SN) in 22q11DS using resting-state fMRI and DTI. Furthermore, we investigated if triple network impairments were related to executive dysfunctions or the presence of psychotic symptoms.

Sixty-three patients with 22q11DS and 68 controls (age 6-33 y.o.) were included in the study. Structural connectivity between main nodes of DMN, CEN and SN was computed using probabilistic tractography. Functional connectivity was computed as the partial correlation between the time courses extracted from each node. Structural and functional connectivity measures were then correlated to executive functions and psychotic symptoms scores.

Our results showed altered structural connectivity within the CEN, DMN and SN, while functional connectivity impairments were evident only within the DMN. At the between-network level, a complex pattern of reduced and increased structural connections was observed, while functional connectivity appeared to be more preserved. Structural connectivity impairments were also related to executive dysfunctions. Based on these findings, we suggest that triple network impairments are responsible for cognitive alterations in patients with 22q11DS. Thus, 22q11DS and schizophrenia share common psychopathological mechanisms.
Heartbeat-enhanced virtual reality alleviates chronic pain in complex regional pain syndrome

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Introduction: Complex regional pain syndrome (CRPS) is a chronic painful condition, whose mechanisms are poorly understood and which difficult to treat. Recent work suggest that manipulating body related signals may alleviate pain in different pathological conditions. Here we manipulated cardiac and visual bodily signals to reduce chronic pain in CRPS patients.

Methods: 24 orthopedic patients with CRPS were tested. We briefly exposed them (90’ repeated 3 times) to cardio-visual stimulation through a physiologically-enhanced virtual reality system, in which we presented with a virtual hand flashing in synchrony (or our of synchrony in the control condition) with their own online-detected heartbeat. We assessed pain, grip strength and heart rate variability (HRV, which is known to be reduced in chronic pain) to measure the analgesic effects of cardio-visual stimulation.

Results: Our data show that pain rating was significantly reduced in the synchronous cardio-visual as compared to the control (asynchronous) condition. Grip strength on the affected hand also selectively increased after exposure to the synchronous condition. Importantly, HRV was significantly higher during synchronous cardio-visual stimulation, similarly as previously reported after analgesics administration.

Conclusion: This study represents a proof-of-concept demonstrating through subjective (i.e. pain rating), functional (i.e. force strength) and physiological (i.e. HRV) measures that exposure to a bodily-specific cardio-visual stimulation can reduce chronic pain in CRPS patients. The use of this physiologically-enhanced virtual reality approach can be applied as long-term treatment of CRPS symptoms, potentially leading to new non-invasive, analgesic rehabilitation programs for different pain conditions.
Vulnerability to cocaine addiction in the Roman High- and Low- avoidance Rats and Involvement of D2 and D3 receptors in Cocaine Seeking- Behaviour After Chronic Self-Administration

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Vulnerability to cocaine abuse has been linked to novelty seeking (NS) and impulsivity personality traits, which in turn have been associated with availability of striatal dopamine D2/3 receptors (D2/3R). Besides, D2/3R have been shown to play a critical role in cocaine addiction. The aim of our study was to validate a rat model displaying different dopamine-related phenotypic traits for observing their susceptibility to cocaine, and to test the specific involvement of D2R and D3R on cocaine seeking.

We used the Roman High- (RHA) and Low- (RLA) avoidance rats’ lines that show different phenotypes for impulsivity and NS. Fifteen rats per line were trained for cocaine (0.4mg/kg/infusion) self-administration (SA) for 15 days. Then, responsiveness to different doses was tested, followed by an extinction phase. Finally, reinstatement of cocaine seeking was tested with non-contingent priming injections of cocaine and quinpirole, a D2/3R agonist, at early (right after extinction) and late (4 weeks thereafter) withdrawal. We then assessed the effects of selective D2R (L-741,626) and D3R (SB-277,011A) antagonists on cocaine-primed reinstatement of drug-seeking.

Results showed that RHAs stably reached significantly higher levels of SA than RLAs, and displayed a vertical shift of their SA dose-response function as compared to RLAs, indicating a higher vulnerability to addiction in RHAs. Cocaine and quinpirole reinstated drug-seeking behaviour in RHAs at both early and late withdrawal. D2R blockade antagonized reinstatement of cocaine seeking-behaviour at both withdrawal phases, whereas D3R blockade did not, thus suggesting a central role of D2R, but not D3R, in cocaine relapse.
Reward processes, structural connectivity of the reward system and negative symptoms in 22q11.2DS

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Background: Alterations of the reward system have been proposed as one of the core mechanisms underlying the expression of negative symptoms in schizophrenia. Deficits in specific reward components and white matter integrity of the reward system have been highlighted in schizophrenic patients. In 22q11.2 deletion syndrome (22q11DS) no studies yet investigated the putative link between negative symptoms and the hedonic experience, or structural connectivity of the reward system.

Methods: This study examined the anticipatory and consummatory dimensions of pleasure in participants with 22q11DS (N=54) and healthy controls (N=55). In the 22q11DS population, the association between the pleasure scores and positive or negative symptoms was investigated. Furthermore, white matter integrity of the accumbofrontal tract was quantified using Diffusion Tensor Imaging (DTI). Associations between DTI measures, pleasure dimensions and negative symptoms were examined.

Results: Patients with 22q11DS showed reduced anticipatory and consummatory pleasure compared to controls. Furthermore, anticipatory pleasure scores were negatively correlated to negative symptom severity in 22q11DS. White matter (WM) microstructural changes of the accumbofrontal tract in terms of increased fractional anisotropy (FA) and reduced radial anisotropy (RD) were also identified in the patients. However, no significant correlation between the DTI measures and pleasure dimensions or psychotic symptoms was observed.

Conclusions: This study revealed that participants with 22q11DS differed in their experience of pleasure compared to controls. The anticipatory pleasure component appears to be related to negative symptom severity in the patients. Alterations of WM integrity of the accumbofrontal tract seem to be related to myelination abnormalities in patients with 22q11DS.
**Redox dysregulation in schizophrenia: development of novel peptide-based drugs**

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Novel peptide-based drugs made from cysteine were synthetized. As N-acetyl-cysteine (NAC) they should have a positive effect on the redox and glutathion regulation. They are currently tested with the auditory evoked prepulse inhibition of the startle reflex, an animal model which is related to schizophrenia.
Neuron-glia interactions

Evaluation of the receptor-mediated function of lactate in neuronal activity.

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The recent discovery of a Gi protein-coupled receptor 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. However, the expression pattern of HCA1R in the brain is still unclear. In addition, the absence of an antagonist for HCA1R makes it difficult to evaluate its functional role. In this study, we present evidence that HCA1R is present and functional in the brain. By assessing the HCA1R mRNA transcript expression in mice using qRT-PCR, we showed that HCAR1 is indeed present in several brain regions. In a reporter mouse line which expresses a red fluorescent protein (mRFP) under the control of the HCA1R promoter, we could identify different brain regions in which HCA1R is expressed. At the functional level, L-lactate and 3,5-DHBA, a non-metabolized agonist of HCA1R, reversibly decreased by 40% spontaneous spiking activity of primary cortical neurons of wild-type mice. Neither compounds affected the activity of neurons prepared from HCA1R knock-out animals, which demonstrates the requirement of HCA1R activation and the non-metabolic nature of the lactate effects on neuronal activity. These results provide strong support for the expression of HCA1R in the mouse brain and for its role as modulator of neuronal network activity.
A key role of astrocytic lactate in the formation and maintenance of memories associated with cocaine-associated cues

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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 positive affective memories associated with cocaine-associated 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 300 pmol/side) 15 minutes before conditioning sessions of a conditioned place preference (CPP) failed to exhibit a clear cut preference for side previously paired with cocaine. To assess the importance of astrocyte-derived L-lactate in the maintenance of CPP another group of rats received a double injection of DAB 15min before and 5h after a re-exposure to the context. This double administration abolished the cocaine attractiveness for up to two weeks. Finally, we demonstrated that drug memory was rescued by L-Lactate co-administration through a mechanism requiring the synaptic plasticity related transcription factor Zif268, and extracellular signal-regulated kinase (ERK) signaling pathway. We then targeted the prefrontal cortex (PFC), rats were injected with DAB (480 pmol) into the PFC fifteen minutes and twelve hours after the contextual re-exposure and then exhibited a significantly reduced exploration of the cocaine compartment. Taken together, these results highlight a signaling role of astrocytic lactate in both acquisition and maintenance of cocaine-seeking behavior following a BLA-PFC temporal pathway.
Development and Characterization of an Extracellular Potassium Nanosensor

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Changes in the extracellular concentration of potassium ([K⁺]₀) have a large functional impact on the brain; for example they affect membrane potential, K⁺ equilibrium potential, and synaptic transmission. Increases in [K⁺]₀, such as those which occur during neuronal activity, are largely controlled for by astrocytes, since these cells are in charge of maintaining K⁺ homeostasis through the uptake of K⁺ from the extracellular space and its redistribution through the syncytium. In addition, K⁺ has been shown to play a role in several more complex processes, such as modulating glutamate transporter activity and stimulating astrocytic glycolysis. To better understand these [K⁺]₀ fluctuations and to gather spatiotemporal data regarding K⁺ related events we developed an extracellular potassium sensitive fluorescent nanosensor. Our nanosensor design consists of an ion sensitive fluorescent dye encapsulated in a nanoparticle. Here we report on the generation and characterization of the nanosensor, including its spectral properties, its sensitivity, and its selectivity for K⁺ and Na⁺. The in-vitro characterizations of the nanosensor’s kinetics, as well as its stability and sensitivity for two photon imaging of [K⁺]₀ in brain tissue demonstrates the effectiveness of the nanosensor strategy. This novel approach of optical imaging of [K⁺]₀ paves the way for future investigations into a wide range of [K⁺]₀ mediated effects.
Exploring the complexity of 3D calcium dynamics in astrocytes

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UNIL-DNF

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. However, the structural-functional complexity of astrocytes makes these cells methodologically challenging to study (reviewed in Volterra et al, Nature Rev Neurosci, 15:327-335, 2014). Consequently, many aspects of their calcium encoding remain poorly understood and the corresponding functions controversial.

An important methodological limitation to-date has been the use of conventional 2D microscopy which captures astrocytic calcium activity in a single focal plane, while astrocytes are highly tridimensional cells. Here we present a novel 3D multiphoton imaging approach which overcomes this limitation and allowed us to study, for the first time, calcium activity of entire astrocytes in adult mouse hippocampal slices. To this purpose, we used a fast-scanning 2-photon setup and transgenic mouse lines expressing genetically-encoded calcium indicators under two astrocyte promoters: hGFAP and GLAST. We recorded 3D calcium signals from entire astrocytes in different hippocampal regions and compared their features.

Using this superior methodological approach we could reconstruct whole-cell astrocyte activity maps under basal and stimulated conditions and identify recurrent activity patterns and hotspots. We observed different types of calcium events spreading with heterogeneous and, sometimes, unexpected modalities across the 3D astrocyte, and defined the real spatial-temporal properties of the events involving the cell body or occurring at “interface” regions like the “gliapil” or the end-feet. The emerging picture provides new insight into astrocyte biology.

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Objective: To explore whether repetitive motorneuron Discharges (repMDs) contribute to intracortical facilitation (ICF) and short intracortical inhibition (SICI). Background: Transcranial magnetic stimulation (TMS) leads to repetitive spinal motor neuron discharges (repMNDs). The paired-pulse TMS (PP-TMS) paradigm allows the exploration of the motor cortex physiology, but the precise mechanisms remain undetermined. The triple stimulation technique (TST) and an extended TST-technique including a 4th and 5th stimulation, Quadruple (QuadS) and Quintuple (QuintS) stimulation, respectively, allow a more precise exploration of the central motor conduction and of repMND. Design/Methods: We explored the PP TMS paradigms of short....(SICI) with an inter-stimulus interval (ISI) of 2ms (PP2) and intracortical facilitation (ICF) with an ISI of 10ms in the conventional way (TMS), combined with the TST, the QuadS and QuintS in a randomized design in 20 healthy volunteers. Results: A great number of the total subjects showed single pulse QuadS and QuintS MEP responses, namely 60% and 40%, respectively. For the subjects showing responses, MEPs were observed in both QuadS and QuintS with a lower prevalence in QuintS. ICF response rate appears to be larger compared to the response rates of SICI and single pulse paradigms both in QuadS and QuintS. The response rate for the SICI paradigm is showed to be smaller than the single pulse paradigm in both Quadruple and Quintuple stimulations. Conclusions: Our preliminary results demonstrate a tendency of more repMND in ICF than in SICI which suggest a possible contribution of spinal motor neuron discharges in the conditioned responses of PP-TMS. There is an inter- and intra -subject variability which needs to be further explored.
Characterization of dendritic structure and dynamics of superficial VIP cells in the mouse somatosensory cortex

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UNIGE - Faculté des Sciences

In the somatosensory cortex of rodents, interneurons consist of a mixed population of cell types. The three non overlapping general categories are: parvalbumin (PV), vasoactive intestinal peptide (VIP), and somatostatin (SOM). PV- and SOM- expressing interneurons synapse onto different parts of pyramidal cells and inhibit them but a large fraction of the VIP-expressing interneurons are thought to connect to other inhibitory neurons. They thereby may serve a disinhibitory function for pyramidal cells. Superficial VIP cells have been reported to receive long-range excitatory input. Many inhibitory neurons are aspiny but recent studies have shown that some subtypes do carry spines, which display structural dynamics similar to those on pyramidal cells. Here we sought to provide insights into the spine dynamics on VIP cells in order to further our understanding of how long-range excitatory inputs may impact local disinhibition.

We used VIP-Cre transgenic mice in combination with Cre-dependent AAV vectors encoding GFP to label and image spiny superficial VIP neurons in the mouse somatosensory cortex in vivo. First we confirmed with immunohistochemistry that the transfected and imaged cells expressed VIP. Reconstructions suggest that the morphology of these spiny cells is multipolar. Longitudinal imaging data suggest that the spine dynamics are different from those on pyramidal cells. We looked into the presynaptic input of superficial VIP cells using transsynaptic tracing and found various long-range inputs among others from the thalamus. In order to investigate a possible role of spine dynamics in experience-dependent plasticity we are currently studying the effects of whisker sensory deprivation.
A novel feeder-free culture system to derive human retinal pigment epithelium from pluripotent stem cells

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The retinal pigmented epithelium (RPE) is a monolayer of pigmented cell located between the retina and the choroid. RPE contributions to the visual process are the recycling of the chromophore required for phototransduction, the phagocytosis of shed photoreceptor outer segments and the regulation of fluid and nutrient flow between. The neural retina activity relies on 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 would be particularly worth to answer these important challenges.

Starting from iPSCs in feeder-free culture conditions we established a three-step protocol able to induce pigmented foci as early as 18 days in differentiation. After a first step consisting on the formation of embryonic body-like aggregates, the neuroephitelium induction follows and then the third phase commit the neural cells to the RPE fate. The cells are characterized by their pigmentation and cobblestone-like morphology, the expression of RPE mRNA markers such as RPE65 (visual cycle), MERTK (phagocytosis), ZO-1 (junctions) or MITF (transcription factor). Protein presence of some of these markers was assessed by immunohistochemistry and phagocytosis ability was investigated by western blotting after photoreceptor segment integration. RPE cells polarization was verified by electron microscopy whereas specific factors secretion was quantified by ELISA assays.

In conclusion, we developed a consistent method to generate hRPE from iPSCs that will be combined to a CRISPR approach to produce in vitro model for RPE deficient-induced retinal diseases.
Time-specific modulations of M1 excitability during motor imagery – a TMS study

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Whether you imagine moving your toes or seeing your favourite landscape, the neural underpinnings involved replicate very closely the processing of the corresponding overt behaviour. Typically, motor imagery activates several nodes of the sensorimotor system, such as the premotor cortex, the basal ganglia, or the supplementary motor area. Nevertheless, the implication of the primary motor cortex (M1) for such imagery task is still highly debated.

To investigate the temporal dynamics of motor imagery, we used the “hand laterality judgement task”, which is known to evoke an unconscious process of motor imagery. By applying single-pulses of transcranial magnetic stimulation (TMS) over the hand motor area of 13 healthy subjects, and measuring the amplitude of the evoked motor responses, we could probe the excitability of M1 at different time-points of the task performance. Using a response-locked approach in order to normalize the substantial inter- and intra-subject variability – which has been overlooked in previous studies - we could reconstruct the temporal dynamics of different muscle-specific M1 subregions.

Our results suggest that unlike overt movement, motor imagery is not restrained to the contralateral hemisphere. Furthermore, they hint at a dual and sequential role of M1 during imagery, with a first, muscle-unspecific process, followed by a second modulation during which relevant muscle-selective activations could be highlighted. In summary, this experiment contributes to a better understanding of the implicit motor imagery process, highlighting its lateralization and specificity, as well as the critical time-windows during which motor imagery interacts with the primary motor cortex.
A cortex dependent reaching task for head-fixed mice

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Reaching out to manipulate objects is fundamental to most of what we do, yet the neuronal circuits underlying remain poorly understood. Previous experiments in primates and rats suggest that frontal cortex plays a key role in this movement, although the organizational details remain controversial. To dissect the neuronal dynamics involved in goal-directed actions a wide range of molecular, optogenetic and optical imaging tools would be necessary. These tools are readily available for mice, but the behavioral paradigms for head-fixed mice are still lacking. Inspired by the classic “center-out” reaching task in primates, we have developed a fully automated behavioral paradigm to study goal-directed reaching in mice. Head-fixed mice were trained to use their forepaw to reach and grab rewards presented at different positions around their snout. After training, mice were able to perform hundreds of successful reaches per session.

To causally dissect the cortical areas involved in this task, we optogenetically silenced specific frontal cortex areas at different stages of the movement. We first inactivated contralateral motor cortex before the initiation of the reaching movement. In this case, the movement was almost completely halted. Secondly, we inactivated motor cortex once the movement had already started. Surprisingly, the reaching trajectory was altered mid-movement, preventing the mouse to reach the reward.

These experiments illustrate that head-fixed mice can be trained on reaching task with multiple positions. We were able to confirm that in mice, as in primates, motor cortex plays a key role not only in initiating, but also executing reaching movements.
Optogenetic loss-of-function mapping of cortical motor circuits involved in voluntary action

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The motor cortex consists of several interconnected subregions playing roles in specific aspects of voluntary movements. A classical approach to attribute function to specific brain areas is local inactivation. However, most silencing techniques are irreversible, invasive or lack the behaviorally relevant time and spatial resolution. In order to overcome these limitations, we developed a non-invasive optogenetic approach to inactivate cortical activity in head-fixed mice.

We trained mice to discriminate between two vibrotactile stimuli and report their answer by pushing or pulling a joystick after a delay period followed by a go cue. Correct answers were rewarded with water. Mice learned the task in 4 to 5 weeks. We tracked forelimb movements and other motor output variables over hundreds of trials per session using an automated behavioral control systems and high-speed video recordings. The different motor areas in the contralateral hemisphere were transiently silenced by activating inhibitory neurons optogenetically through the intact skull using a laser scanning system.

We found that inactivating frontal areas impaired the performance at several levels. Inactivating small areas of the forelimb sensorimotor representation was sufficient to impair discrimination ability during stimulus presentation. More extended cortical inactivation was necessary to affect choice during the delay period. Finally, after the go cue, only specific aspects of the movement kinematics, but not choice parameters were affected by cortical silencing.

These results confirm the important role that different frontal cortex circuits play during the different phases of decision making, planning and execution of goal directed forelimb movements in mice.
Signalling and Excitability

Investigating the role of the serotonin receptor 3A in limbic brain oscillations

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In humans and rodents the serotonin system interacts with early-life stress (ELS) to modulate stress-related phenotypes. Recently, we found that early life adversity affects the methylation of the serotonin 3a receptor (Htr3a) in an allele-specific manner (Perroud et al. 2016). In addition, we found that ELS interacts with the Htr3a to modulate anxiety-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), the ventral hippocampus (vHPC) and dorsal hippocampus (dHPC). Previous findings in the field suggest that the mPFC-vHPC connectivity regulates anxiety states. Here we first aimed to investigate the role of the Htr3a in mPFC-vHPC functional connectivity during resting state. To do this, we performed intra-cortical electrophysiological recordings in head-fixed wild-type and Htr3a-ko mice and analyzed local field potentials in mPFC, vHPC and dHPC. Preliminary data indicate increased power in the theta range specifically in the prelimbic mPFC but not vHPC or dHPC of Htr3a-ko mice, suggesting a neuromodulatory role of the serotonin system on mPFC theta oscillations. Given these initial results, we aim to use chemogenetic and optogenetic tools to investigate the role of Htr3a-mediated serotonin signaling on brain oscillation in the mPFC and to link these manipulations with anxiety-like behavioral readouts.
Glutamatergic synaptic recruitment of thalamic reticular nucleus by postsubicular afferents: role in head-direction system?

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The thalamic reticular nucleus (TRN) is a cornerstone of attentional mechanisms as it modulates state-dependent interactions between thalamic circuits and sensory cortices. The anterior portion of the TRN is connected to limbic structures, yet little is known about its role in thalamocortical communication. Identification of novel afferents to the TRN could bring insight on unknown functions of this strategically positioned nucleus.

Retrobead and Phaseolus injections in mouse brains revealed postsubiculum (PSub) projections to the anterior portion of both TRN and thalamus (AThal).

TRN and AThal neurons discharge in a time-locked manner in response to postsubicular afferent activation in in vitro acute brain slices. Minimal optogenetic stimulation revealed a four-fold greater connectivity at PSub-TRN synapses than at PSub-AThal. Both afferents showed little short-term plasticity, even during train stimulation, which lead to persistent membrane depolarization and enhanced/maintained discharge propensity.

In urethane-anesthetized mice, light stimulation of the PSub triggered rebound burst firing in TRN neurons. Freely moving in vivo data showed different light-evoked responses along the postsubicular-thalamic axis: fast excitation, delayed excitation, suppression of firing.

Together, these data identify a faithful information transfer between PSub and thalamic circuits, including TRN.

The AThal/PSub circuit is involved in the Head Direction (HD) signal, an essential component of the self-referenced navigation system. Neurons encoding for HD are most prominently found within these two structures. Although the TRN controls all dorsal thalamus through feedforward inhibition, its role in the HD system remains largely unexplored and will be investigated in this study.
Oxytocin receptor signaling in the prefrontal cortex modulates the inhibition of fear responses by the amygdala.

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The projections from different areas in the medial prefrontal cortex (mPFC) to the amygdala modulate fear expression and extinction. The prelimbic cortex (PL) projects to the basolateral area of the amygdala (BLA) and facilitates the retrieval of fear. Here, we hypothesized that the oxytocin receptor (OTR) modulates this pathway.

In the mPFC, OTR have been found in somatostatin positive cells, a type of interneurons (INs) that inhibit the dendrites of pyramidal neurons, but also the parvalbumin positive neurons. Thus, the OTR signaling could be involved in an inhibitory/desinhibitory circuit within the mPFC, regulating the fear retrieval projections to the amygdala.

We traced the projections form the prelimbic cortex (PL) to the basolateral amygdala by retrograde labeling; this tracing technique was coupled with patch clamp recordings, in order to identify the sensitivity of amygdala projecting neurons in the mPFC to oxytocin. OTR activation in fluorescent cells within the PL (L5) increases IPSC frequency, and this effect is blocked with the OTR antagonist. This suggests that the OTR signaling could inhibit the projections from PL to BLA, and therefore, reduce fear expression during retrieval.

Moreover, in vivo inactivation of OTR in the PL during fear conditioned/avoidance learning increases fear expression measured as freezing behavior and the latency to avoid the footstock after conditioning, while decreasing avoidance behavior.

In addition, since the OTR is expressed by somatostatin interneurons, with the use of an AAV-SST-RFP construct we are able to identify these cells to perform patch clamp recordings during the pharmacological activation of OTR.

Taken together, these results support the idea that the OTR promotes the inhibition of pyramidal neurons in the PL, consequently, the fear projections to the amygdala.
Heroin-evoked synaptic plasticity in the accumbens driving cue-evoked relapse

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Synaptic plasticity has been proposed as the neural substrate of addiction and has principally been studied with psychostimulants, mainly cocaine. Here we propose to reevaluate this theory using heroin, a substance belonging to another class of drug, opioids. Despite different molecular targets and mechanisms of action, both drugs share a common endpoint. Specifically, they increase dopamine (DA) levels in the mesolimbic system, especially in the Nucleus Accumbens (NAc). However, the involvement of DA in the reinforcing and/or addictive properties of opioids remains controversial. Another open question concerns heroin-induced synaptic plasticity, which could underlie drug-induced adaptive behaviors, and their similarities and/or differences with the ones induced by psychostimulants.

In the first experiment, using a self-administration (SA) mouse model of cue-associated heroin seeking combined with ex vivo electrophysiology in optogenetically identified circuits, we investigate the input specific (baso-lateral amygdala, medial prefrontal cortex and ventral hippocampus) plasticity of excitatory transmission linked to specific components of addiction-related behaviors. In the second experiment, using a self-stimulation (SS) mouse model we directly test the involvement of DA in the reinforcing properties of heroin. We also test whether the activity of DA receptors (D1 and D2) is necessary in the initiation of heroin-addictive-related behaviors.

Is a DA-dependent mechanism underlying opioids addiction and is the heroin-induced neural plasticity similar as the one induced by psychostimulants? Using cell-type specific transgenic mice lines combined with optogenetics we address these questions aiming to understand the neural basis of opioid addiction. Determining whether opioids and psychostimulants addiction are a same phenomena or behaviourally and neurobiologically different will have important application regarding treatments and addiction theories.
Exploring the full potential of factor analysis for the optimization of voxel-wise parameter estimation and inference analysis with Statistical Parametric Mapping in molecular neuroimaging

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Introduction Voxel-wise estimation of binding parameters in PET and SPECT imaging suffers from high levels of noise. Despite a multitude of proposed denoising approaches, no study has determined the effect of denoising in the ability to detect differences in binding at this level. Methods We performed a study in which groups of subject-images with a 10% - and 20%- difference in binding of [123I]IMZ at the voxel level were simulated. Images were denoised with Factor Analysis (FA) and quantification was performed at the voxel-level. Bias and variance of parametric binding potential (BPND) were evaluated and parametric images were then analyzed using Statistical Parametric Mapping (SPM) to detect group differences. FA was also applied on a series of [123I]IMZ and [11C]FMZ clinical images and the variance of BPND in terms of coefficient of variation (%) was evaluated at the voxel level. Results Estimations from FA-denoised images provided a more favorable bias-precision profile of BPND. An increase by up to 50% in the recovery of simulated voxels with SPM was observed for both simulated increases in BPND. Denoising dynamic clinical SPECT and PET images significantly diminished the variability of voxel-wise binding estimations. Conclusion FA is a powerful tool for noise removal from dynamic SPECT and PET brain imaging studies for optimization of voxel-wise BPND estimations and detection of biologically meaningful differences at the voxel-level.
Improvement of Interictal Epileptiform discharges detection during EEG-fMRI: Pulse Artefacts correction based on Non-Local Means filtering.

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Introduction: One of the main artefacts during simultaneous EEG-fMRI is the Pulse Artefact (PA), deriving from electrodes and wires motion in the magnetic field subsequent to heartbeats. PA removal is usually performed by Averaged Artefact Subtraction (AAS). This approach doesn't account for the beat-to-beat PA variability and gives rise to important residuals, especially at high field. This study aims to test the performance of a non-local mean (NLM) filtering where all PA occurrences are considered into the averaging with a weight depending on their similarity.

Methods: EEG was acquired at 3T and at 7T using a 256- and 64- channels system in a healthy subject and an epileptic patient. For the NLM algorithm, for each channel, a distance matrix was built by computing the L2-norm between each pair of PA occurrences. This matrix was used to weight the artefacts averaging. PA was corrected by AAS and NLM. The amplitudes of the Global Field Power (GFP) of the corrected EEG normalized to the amplitudes of the correspondent GFP peaks in the not-PA-corrected EEG were used to compare the corrections. Moreover, IEDs of the patient were averaged to assess the preservation of the EEG signal after AAS and NLM corrections.

Results: PA residuals were smaller in amplitude for NLM than for AAS. The average improvements of NLM on AAS were: 16% for the healthy subject at 3T and 7T; 7% and 3% for the patient at 3T and 7T. IEDs of the patient were preserved and resulted in the same topographic map.
Evaluation of Redox Dysregulation in the Pathology of Schizophrenia Using Induced Pluripotent Stem Cell Technology

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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.
Astrocyte cell volume and ionic homeostasis are challenged by neural activation: a multimodal approach

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Among the many active roles played by astrocytes, we can mention K+ clearance and glutamate uptake from the extracellular space (ECS) during neuronal activation. 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⁺].
Quantitative analysis of the structural organization of the monkey entorhinal cortex.

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The superficial layers of the entorhinal cortex represent the main entry ways for the sensory information processed by the hippocampus, whereas its deep layers provide the main exit ways through which processed information is sent back to the neocortex. Interestingly, the number of neurons contributing to these pathways varies between subdivisions of the entorhinal cortex. In Eo, 10% of neurons are in layer II, 74% in layer III and 16% in layers V and VI. In Er, 10% of neurons are in layer II, 55% in layer III, 9% in layer V and 26 % in layer VI. In Ei, 13% of neurons are in layer II, 41% in layer III, 15% in layer V and 31 % in layer VI. In Elr and Elc, 17% of neurons are in layer II, 38% in layer III, 15% in layer V and 30 % in layer VI. In Ec, 15% of neurons are located in layer II, 38% in layer III, 15% in layer V and 32 % in layer VI. In Ecl, 21% of neurons are in layer II, 39% in layer III, 13% in layer V and 27 % in layer VI. These data suggest that (1) the rostral entorhinal cortex might project more heavily to CA1 via projections from layer III neurons; (2) projections from entorhinal cortex layer II neurons to the dentate gyrus might increase from rostral to caudal; (3) the targets of return hippocampal projections within the deep layers of the entorhinal cortex might be more prominent caudally.
Multimodal detection task during wide-field calcium imaging of mouse neocortex

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Even simple behaviors, such as perceptual decision-making, require distributed and complex communication between several brain areas that are used to elicit appropriate motor commands. It is therefore interesting to use techniques that allow chronic recordings of whole cortex activity throughout the entire learning process to better understand sensory-motor transformation. In this study, head-restrained water-restricted mice learnt to lick a spout after either a brief whisker deflection or an auditory beep in order to be rewarded with a drop of water. To image cortical activity on the brain surface over several days of training, transgenic Thy1-GCaMP6f and Emx1-GCaMP6f mice were used. Calcium signals were recorded using wide-field fluorescence microscopy connected to a high-speed CMOS camera. The high temporal resolution and large spatial scale that this technique offers, allows to resolve rapid and complex cortical activity dynamics in awake behaving mice. Preliminary results show that a rapid response occurs briefly after stimulus onset in primary sensory cortices for both hit and miss trials. In hit trials, we observe rapid spread of activity to frontal regions, i.e. whisker primary motor cortex M1, followed by a long-lasting brain-wide depolarization during a second phase. These results indicate a rich interaction between sensory and motor areas that could play a key role in performing the task.
Functional Organization of the Visual Cortex of Microcebus Murinus

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The prosimian mouse lemur (Microcebus murinus) belongs to the World’s smallest primates (~60gr). Due to its relatively quick reproduction and good cognitive capacity, this prosimian has the potential to become an interesting primate model for systems neuroscience. In their native habitat, the forests of Madagascar, mouse lemurs are active at night, frantically foraging for insects, small vertebrates and fruits. The impressive leaps and fast chases through the dense vegetation under dimly lit conditions suggest that they possess a highly developed visual system. How the visual information is represented and processed at the cortical level is currently unknown. From an evolutionary perspective, their small size raises the question if classical primate features such as orientation preference maps exist in a rodent-sized brain. This project aims to adapt cutting-edge, systems neuroscience rodent tools to investigate the functional organization of visual cortex in this small primate.
Layer-specific thalamocortical input onto excitatory neurons in mouse primary somatosensory barrel cortex

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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 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. The onset latencies were shortest in L4 and L5A for VPM and POM input respectively. Our results begin to provide a more complete understanding of the distribution of thalamic input onto excitatory neurons across the layers of the mouse barrel cortex.