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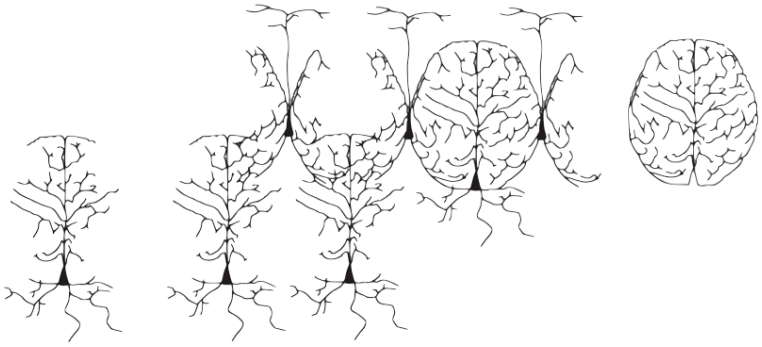

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Autonomic, Limbic, Neuroendocrine or Other Systems

Mixed transmission in a mesohippocampal projection

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UNIGE - CMU

The ventral tegmental area (VTA is a core component of the mesolimbic reward circuit, essential for learning the association between predictive stimuli and motivationally-relevant outcomes. While VTA dopamine neuronal connectivity has been extensively studied, the fewer represented GABAaergic population has received considerably less attention. We report here the identification of a VTA neuronal population that sends a long-range, functional projection to the hippocampus in the mouse. Using a combination of optogenetic tools, retrograde tracing and electrophysiological recordings in vitro, 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 sensitivity to both bicuculline and NBQX, suggesting a possible corelease of GABA and glutamate from these mesohippocampal terminals. Finally we show that this projection is functional in vivo and its stimulation leads to a reduction in granule cells' firing rate in anesthetized animals. Altogether, the present results describe an unreported connection between VTA and hippocampus mediated by mixed GABA/glutamatergic neurons, thus providing a deeper insight into the reward system connectivity.

Insular cortex involvement in the metabolic tuning of anxiety

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UNIFR

Nutritional signals are known to influence behavior. Studies in Humans have highlighted changes in cortical activity during fluctuations of metabolic states. These activity patterns are correlated with modulations of emotional and cognitive outputs. Despite their important clinical relevance, the presence of cortical circuits matching body metabolic signals and behavior has been little explored. In this project, we are investigating the role of the insular cortex (IC) as an interface between interoceptive sensing and emotional responses.

In vivo fasting decreased anxiety-like behaviors in mice and increased cfos expression in IC. In parallel, injection of tetrodotoxin in mice IC led to an increase in anxiety-like behavior. These data suggest the presence in IC of metabolic-sensing circuits that could modulate anxiety.

To investigate these circuits more in detail, we performed immunohistochemical labeling with molecular markers of cells subtypes and cortical localization. In addition, we used an activity reporter mouse model to tag metabolic-responsive cells of IC and analyze their response mechanisms to metabolic cues with whole-cell electrophysiology and calcium imaging. Furthermore, this model will enable us to manipulate the activity of metabolic-responsive cells by opto- or chemo-genetics to determine their causal role in anxiety-like behavior.

Behaviour, Cognition, Neuroimaging

Spatial working memory deficits in aging: Is it that bad?

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Working memory, the system that keeps limited amounts of information for brief periods of time to guide behavior, is vulnerable to normal aging. However, spatial working memory, essential in daily activities such as learning new routes or driving a car, is thought to be particularly affected in normal aging. Here, we performed an experiment to test the specificity of this purported age-related decline in spatial working memory, in a real-world allocentric spatial memory task. We tested 24 healthy elderly (65-75 years) and 24 young adults (20-30 years) in an open-field memory task under different conditions designed to compare four types of memories (spatial working memory, color working memory, spatial reference memory, color reference memory), under different memory loads (one, two or three items to remember). We used two distinct measures to characterize memory performance: the number of correct choices before erring, an estimate of memory capacity; and the number of errorless trials, an estimate of perfect memory. We found: (1) a general decline of memory performance with age, (2) a greater deficit in working memory than reference memory, independently of the type of information, (3), a greater deficit of spatial reference memory than color reference memory, but (4) no evidence that spatial working memory was more affected than color working memory. These results suggest that different types of memory are differentially affected in aging, but that the deficits in memory performance are linked to the representational demands of the task and not to the type of information to be remembered.

Does my brain want what my eyes like - How food liking influences choice and impacts spatio-temporal brain dynamics of food viewing

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The influence of valuation on food-related decision-making and their impact on visual food perception remains poorly understood, although being of great interest for body weight management. Our study investigated behavioral aspects and spatio-temporal brain dynamics related to the viewing of pairs of food images in twenty-two normal-weight participants. Participants were asked to rate their liking for each food item (valuation phase) and to further choose between the two alternatives (choice phase). Further, visual evoked potentials (VEPs) were assessed. Behaviorally, highly liked foods were chosen most often, and also rated faster than mildly liked or disliked foods. At the brain level, the level of liking as well as the subsequent choice modulated VEPs as early as 135-180ms after food image onset. Estimation of neural source activity patterns over this time period showed an interaction between liking and choice within the insula, the dorsal frontal and the superior parietal regions. Yet, modulations by liking were apparent only when the viewed food had been chosen over an alternative. Therein, neural responses to disliked foods were found to be stronger than those to food images that were liked more, showing that the spatio-temporal brain dynamics to food viewing are immediately modulated by both the liking of foods and subsequent choices. These valuation and choice processes occur in brain regions involved in salience and reward attribution as well as in decision-making processes, thus likely influencing daily food choices.

No influence of emotion on orbitofrontal reality filtering

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Orbitofrontal reality filtering is a preconscious memory mechanism that allows keeping our thoughts in phase with reality by filtering memories and thoughts that do not relate to the ongoing present. Electrophysiologically it is expressed at 200-400 ms after stimulus presentation. Deficits to this mechanism induce reality confusion, confabulations and disorientation. It is unknown whether and how emotions influence the sense of present reality. Here we tested the influence of positive emotions on the behavioral and electrophysiological characteristics of reality filtering. We used a continuous recognition task composed of two runs, the first one testing recognition capacity and the second one reality filtering. Pictures were either neutral or positive. Nineteen healthy subjects performed the task while high resolution evoked potentials were recorded. Performance was more accurate and faster on neutral than positive pictures, irrespective of run or required response type. Thus, emotion did not influence reality filtering. ERP correlates of emotion and of reality filtering occurred at 280 – 350 ms but dissociated in terms of waveform amplitudes and topography. We conclude that reality filtering is not influenced by the emotionality of memories. This result is consistent with the clinical observation of confabulations' content in reality confusing patients, which mainly refer to daily habits rather than emotionally salient events.

Infra-slow neural and cardiac fluctuations predict behavioral arousability during NREM sleep

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Environmental noise at night disrupts sleep and adversely affects general health by causing daytime sleepiness and increasing cardiovascular risk factors. This calls for a profiling of sleep in terms of fragility to acoustic disturbance and in association with cardiovascular activity. Here we show that noise-induced arousal is specifically predicted during mouse non-rapid-eye-movement sleep by an infra-slow fluctuation (periodicity ~45 s) in the power of sleep spindles, a 10-15 Hz electroencephalographic rhythm implied in sleep's beneficial actions on memory formation, which is phase-locked to slow components of heart rate variability. By choosing an acoustic stimulus such that mice wake up or sleep through noise at comparable rates, we discovered that, prior to noise onset, sleep spindle power peaked when an arousal followed. Conversely, sleep-through was preceded by a trough in spindle power, concurrent with augmented heart rate fluctuations. Infra-slow fluctuations occurred in sensory and associational cortical areas and were suppressed by zolpidem, a widely used hypnotic drug, substantiating their role as sleep fragility markers. Varying arousability hence arises from joint central autonomous and sleep-wake control mechanisms, going beyond traditional views of thalamocortical sensory gating. Together, we show for the first time that arousability during mammalian sleep fluctuates constantly due to a specific brain-heart crosstalk. The coordination between a salient sleep rhythm and an index for cardiac health bears the potential for assessing the pathophysiological links between sleep disorders, cognitive deficits, and cardiovascular disturbance.

Effects of theta-burst stimulation on word learning

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Introduction: Repetitive transcranial magnetic stimulation (rTMS) is a promising neuromodulation technology which may be able to enhance naming performance. However, the effect of rTMS on brain organization and clinical recovery are insufficiently understood. The aim of this sham-controlled study was to assess the effects of continuous theta burst stimulation (cTBS) on learning new vocabulary in healthy participants.

Methods: 16 participants were alternatively trained in two picture naming lists after cTBS or sham stimulation applied to the right inferior frontal gyrus (IFG). One day after each training session, the increase in correctly named pictures in comparison to baseline was measured. To characterize neural changes, we performed event-related functional connectivity as well as event-related potential and event-related power analysis at the source level. Finally, we investigated their association with naming performance.

Results: On the behavioral level, participants showed no significant difference between cTBS and sham stimulation ($p=0.67$). On the neural level, the naming task induced a significant increase in high-gamma power (55-95 Hz) at a left temporo-occipital region between 400 and 800 ms after stimulus presentation ($p<0.05$, FDR corrected). One day after cTBS-modulated learning, event-related delta and theta power at this area was significantly enhanced, while it was reduced one day after sham stimulation followed by learning ($p<0.05$, FDR corrected).

Conclusions: Neural power changes induced by lexical learning can be modified by one session of cTBS, and this effect persists at least one day after stimulation. Nonetheless, these neural changes do not necessarily translate into improved learning performance in picture naming tasks.

How reward conditioning affects subsequent learning: Generalization and deactivation.

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Expectation of reward produces a state of motivation that enables reward-predictive learning. In this process, functional interactions between the medial temporal lobe and striatum enhance memory for rewarded information. Yet, it is unclear whether memory advantage for rewarded stimuli is maintained when stimuli are first rewarded and then used in a memory task. We designed an fMRI experiment to test whether reward conditioning influences hippocampus-dependent learning in a subsequent task, and whether reward value may transfer from the specific rewarded cues to semantically related ones.

Reward conditioning was successful: high (vs. low) reward cues evoked higher activation in the ventral tegmental area (VTA). Data from the picture-location memory task revealed effects of prior reward conditioning. Firstly, the ventral striatum (VS) and the hippocampus showed reduced activity during the encoding of subsequently remembered picture-locations for pictures belonging to the previously rewarded semantic category (both old and new ones). In addition, the distance to target (i.e. the degree of error) on a given trial was proportionate to the activation in the VS during encoding of high-reward associated pictures throughout the task with generalization to new semantically-related pictures early in the learning. Secondly, source memory accuracy 24h later was enhanced for all reward-related pictures. Accuracy in the picture-location learning task was modulated by individual trait reward-responsiveness such that higher reward-responsiveness led to better performance for high-reward pictures.

Our results show that reward association may support later memory formation in reward-sensitive individuals, even when no actual monetary reward is delivered in the learning context.

Rhythmic sensory stimulation of the thalamocortical circuitry in mice and its effects on sleep homeostasis

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Rhythmic sensory stimulation (0.25Hz), broadly known as “rocking”, has been recently demonstrated to facilitate the transition from wakefulness to sleep and to increase slow wave (1-4Hz) and spindle (11-15Hz) EEG activity in healthy humans features of sleep that have been associated with sleep homeostasis. 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.

C57BL6/J mice, implanted with EEG/EMG electrodes, were shaken in the horizontal plane during the main sleep period at three different frequencies (0.25Hz, 1Hz and 1.5 Hz), during the main sleep period (i.e., the 12-hour light period). The EEG/EMG signals were recorded continuously for two consecutive stationary days, one “rocking” day and another stationary day, for each frequency. Shaking at 1Hz recapitulated the observations in humans, thus indicating that rhythmic sensory stimulation promotes NREM sleep also in the mouse. Moreover, the main effects took place mainly in the first three hours after the start of shaking. To further evaluate the effect on sleep onset latency, mice were kept awake for 1h, four hours after light onset, followed by “rocking” for the remainder of the light period. Sleep onset latency was reduced when the mice were rocked at 1Hz.

Thus, we have established a mouse model allowing us to investigate the mechanisms by which “rocking” impinges on the sleep circuitry. The results could help develop a non-pharmacological intervention for people suffering from sleep disorders.

The circadian gene PER2 responds to spontaneous changes in sleep-wake state

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UNIL-CIG

Sleep-wake rhythms are orchestrated by the interaction of a homeostatic and a circadian process. While the SCN are required for circadian rhythms in overt behaviors, at the cellular level, clock genes, such as Period2 (Per2), engage in transcriptional/translational feedback loops resulting in rhythmic gene expression with periods of ca. 24h. Accumulating evidence demonstrates that these clock genes, besides their role in circadian rhythm generation, also play a key role in sleep homeostasis; e.g., central PER2 levels increase during enforced wakefulness and decreases during recovery (Curie et al., SLEEP 2015). If a similar phenomenon also occurs during spontaneous waking and sleeping, could, however, not be studied due to lack of appropriate methodology. Saini and colleagues (Genes Dev 2013) developed a device allowing us to measure PER2 levels at a high time resolution in a freely behaving mouse, along with EEG recordings. As expected, PER2 oscillated in circadian fashion in the periphery, increasing during the active phase, and decreasing during the rest phase. Additionally, our preliminary analysis shows that PER2 is increasing during waking bouts and decreasing during sleeping bouts, indicating the substantial contribution of sleep-wake state in PER2 levels. This finding should be kept in mind when using clock-gene rhythms as state variables of the circadian clock.

Meta-analysis of real-time fMRI neurofeedback studies: how is brain regulation mediated?

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An increasing number of studies using real-time fMRI neurofeedback have demonstrated that successful regulation of neural activity is possible in various brain regions. In an effort to detect regions that are responsible for the act of brain regulation itself,independent of the target region choice, we performed a post-hoc analysis of data involving different target regions based on studies from different research groups.
We included twelve suitable studies that examined eight different target regions amounting to a total of 175 subjects and 899 neurofeedback runs. Data analysis included a standard first- (single subject, extracting main paradigm) and second-level (single subject, all runs) general linear model (GLM) analysis of all participants taking into account the individual timing. At the third level, a random effects model GLM included all subjects of all studies, resulting in an overall mixed effects model.
The analysis revealed that the anterior insula, important for interceptive awareness and cognition, as well as the basal ganglia, that are implicated in procedural learning, visuomotor integration and motivation, were consistently active during the regulation of brain activation independent of the targeted region-of-interest. Our results imply that if the real-time fMRI neurofeedback studies target regions of this regulation network, such as the anterior insula, care should be given whether activation changes are related to successful regulation, or related to the regulation process per se. Furthermore, future research is needed to determine how activation within this regulation network is related to neurofeedback success.

Predictability, efference copies, and non-retinotopic motion

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Perception is usually non-retinotopic. For example, a reflector on the wheel of a bicycle is perceived to rotate on a circular orbit, while its retinotopic motion is cycloidal.
To investigate non-retinotopic motion perception, we used the Ternus-Pikler display. Two disks are repeatedly flashed on a computer screen. A dot moves linearly up-down in the left disk and left-right in the right disk (retinotopic percept). If a third disk is added alternatingly to the left and right, the three disks form a group moving predictably back and forth horizontally. The dot in the central disk now appears to move on a circular orbit (non-retinotopic percept), because the brain subtracts the horizontal group motion from the up-down and left-right motion.
Here, we show that predictability is not necessary to compute non-retinotopic motion. In experiment 1, the three disks moved randomly in any direction. In experiment 2, we additionally varied the shape and contrast polarity of the stimuli from frame to frame. In both cases, strong non-retinotopic rotation was perceived. Hence, the visual system can flexibly solve the non-retinotopic motion correspondence problem, even when the retinotopic reference motion is unpredictable and no efference copy-like signals can be used.

EEG auditory discrimination in acute coma predicts long-term quality of life

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CHUV

A recent study showed that improvement of auditory discrimination over the first two days of coma in post-anoxic comatose patients is informative of survival. Here we investigate whether auditory discrimination in acute coma can be predictive of long-term cognitive and functional outcome. Electroencephalography (EEG) recordings were performed twice for 56 post-anoxic comatose patients using a 19-channel clinical electrode montage during a Mismatch Negativity (MMN) paradigm; the first within 24h after cardiac arrest under therapeutic hypothermia, the second within 72h, after return to normal temperature. Auditory discrimination was quantified using single-trial topographic EEG analyses. At 6 months, survivors performed an exhaustive neuropsychological interview assessing cognitive functions and quality of life. Twenty-eight of the 56 patients recorded survived at 6 months (52%), and 25 (89% of survivors) answered a quality of life questionnaire. Eleven of them (44%) showed improvement of auditory discrimination during acute coma (6 women; mean age: 56±15 years), and 14 (56%) not (4 women; mean age: 54±14 years). Two-tailed independent sample t-test revealed a significant difference between these two groups concerning quality of life satisfaction ($t(23)=2.24$; $p=0.04$), with survivors accurately predicted by the MMN paradigm reporting higher quality of life satisfaction (mean score: 86±11) as compared to those not predicted (mean score: 71±20). This difference was not explained by clinical or demographical variables. Conversely, cognitive outcome tended to be better in survivors not predicted by the MMN paradigm ($n=23$; $t(21)=1.99$; $p=0.06$). These results suggest that improvement of auditory discrimination in acute coma provides relevant information about long-term functional outcome.

Confident misunderstanding: examining the neural correlates of the metacognition of emotion recognition

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Previous research suggests that people may not have accurate beliefs on how empathically accurate they are, suggesting poor metacognition of emotional face recognition. Moreover, while there is extensive research on the metacognition of perceptual decision-making, the neural substrates pertaining to metacognition of emotion recognition are yet to be elucidated. To investigate this issue, we used functional MRI and asked participants to either judge the emotion displayed by faces with ambiguous emotional expressions (morphed faces displaying a mixture of happy and angry emotional expressions) or perform a perceptual judgment on two lines placed on the top and bottom of these faces (thicker line on top or bottom). On each trial, participants also rated their confidence on how accurate they believed their previous decision was, without any feedback. Our results show that people display overconfidence and worse metacognition for facial emotion recognition compared to the metacognition of perceptual decision-making. Further, individuals with good metacognitive abilities of emotion recognition showed higher empathy scores. Finally, fMRI data provide new insights into specific neural correlates linked with the metacognition of emotion recognition, in comparison with perceptual decision-making. These data point to a key role for the retrosplenial cortex in metacognitive processes related to emotion recognition. Our findings suggest that RSC is implicated in monitoring processes linked to confidence for emotion recognition, possibly through its role in internally – directed cognition, particularly, in the subjective reflection on emotional states as well as its contribution to self-referential introspective and contextual processes.

How do action video game players and non-action video game players' brains differ at rest? An EEG microstate analysis

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Action video game players (AVGPs) outperform non-action video game players (NVGPs) on a variety of perceptual and attentional tasks. Studies of underlying neural differences have focused so far on task-related activity (Bavelier et al, 2011). The present study aims at investigating neural differences between these two groups at rest, when no particular task is performed. To this purpose, five minutes of eyes-closed EEG (electro-encephalography) were recorded in 10 AVGPs (mean age = 22.8 years) and 9 NVGPs (mean age =22.6 years), following an attention-demanding visual task. Spatial cluster analysis of EEG topographical maps allowed the extraction of stable brain electric activity maps – the so called microstates, which have been suggested to reflect synchronization of large-scale networks and to reflect specific mental processes (Koenig et al., 2005). There are four microstates classes which have been repeatedly found to best represent spontaneous brain electric activity: auditory, visual, self-referential salience and attention-reorientation (Britz et al, 2010). In our data set, the comparison of the dominant microstate maps across groups revealed that one map, typically associated with visual processing in the literature, was much more present in AVGPs relative to NVGPs. The 'visual' map did not only explain more variance in gamers EEG data but its frequency of appearance was also significantly higher in AVGPs. This result is interesting in light of behavioral studies that document superior performance of AVGPs in a variety of visual tasks. Newly acquired resting state data is currently analyzed in a separate sample in order to verify the replicability of the present results.

Bodily Self-Consciousness Overlaps in Angular Gyrus with Episodic Autobiographical Memory: Meta-Analytically Based Investigation

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Objective: The parietal cortex has been involved in a broad variety of cognitive tasks, from spatial processing, to attention, to social cognition and even memory. However, the organization and function of the parietal cortex across different cognitive domains is not well known. A previous fMRI study (Ionta et al., 2011) revealed an anatomical overlap between brain damage in patients with abnormal self-location due to out-of-body experience (OBE) and experimentally induced changes in self-location in healthy subjects in right temporo-parietal junction (TPJ). As such, we wanted to further investigate the involvement of this part of the parietal cortex in different cognitive and bodily self-consciousness related tasks.
Aim: This meta-analysis examines the anatomical overlap of autobiographical memory (i.e. episodic memory, semantic memory and conceptual self) with the representation of bodily self-consciousness and default mode network in order to link the different potential functions of the parietal cortex with bodily self-consciousness.
Methods: Four separate ALE analyses (over 80 papers, 800 subjects and 600 foci) were carried out using GingerALE 2.3 (Laird et al., 2005) in order to define a specific network of activation for each of the cognitive domains. The primary ALE analyses were conducted using FDR correction of $P < 0.05$ with minimum cluster size of 200 mm^3. Furthermore, we wanted to determine the anatomical level of overlap across the cognitive domains together with the previous TPJ lesion and fMRI analysis (Ionta et al., 2011).
Results: Extending on our previous OBE lesion analysis, our current meta-analysis reveals an anatomical overlap across specific cognitive domains (i.e. memory, default mode network) with experimentally induced changes in self-experience.
Conclusions: We show a common network of activity in parietal areas that have been previously found to be specifically involved in episodic memory retrieval and default mode network and the region linked to out of body experience in patients.

Executive functioning in seniors with fall risk

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Falls are common in elderly people aged 65 years and older. Decline in executive function, gait variability and balance have been demonstrated as sensitive predictors of falls. This study combined clinical and fMRI measures to evaluate the executive functions impairment in seniors with fall risks. Secondly, we aimed to determine how falls and walking parameters are related with cognition decline in seniors.

34 community-dwelling seniors took part in a clinical and fMRI study. Clinical study collected data from temporal-spatial gait parameters and neuropsychological tests. To assess executive functions, fMRI sessions involved a motor coordination task (under simple or dual-task conditions) and a selective attention task.

The coordination task results indicate that seniors have more difficulties to perform multitasking. They were slower to answer in the dual-task condition and activated larger patterns of brain activity in dual-task condition compared to the simple conditions. In the attentional task, participants were significantly slower to answer in the incongruent than in the congruent and showed stronger and bilateral activity in areas associated with conflict. Parametric regressor analyses identified several areas where the BOLD signal covariates with clinical parameters.

As predicted, elderly participants have difficulties to inhibit interfering information and performing concurrent tasks. These results suggest greater attentional load to face behavioral challenges due to reduced capacity in executive functions. Our fMRI correlation results indicate that cognitive decline is related to vulnerability in elderly with fall risk, as highlighted by the association between cerebral network recruitment and clinical parameters.

Constitutional differences in glucocorticoid responsiveness to peripuberty stress are associated with differences in psychopathology-like behaviors in rats

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We have previously shown that subjecting rats to peripuberty stress (PPS) induces long-lasting alterations in socio-affective behaviour and that glucocorticoid production and actions can be ascribed a key role in these changes. As corticosterone levels immediately after PPS were found to correlate with expression of dysfunctional behaviours at adulthood, we hypothesised that individual differences in stress responsivity might represent a differential vulnerability for the development of psychopathology following PPS. Starting from a population of outbred Wistar rats, selective breeding of 2 lines was established according to animals' response to two psychogenic stressors across postnatal days 28-30. Rats expressing extremes in plasma corticosterone values at offset of p30 stressors were selected for 'Low-' and 'High-' corticosterone breeding lines. We evaluated socio-affective behaviours in F6 both, following control conditions or exposure to PPS. As compared to the Low-line, animals from the High-corticosterone line spent: (i) less time on the open arms of an elevated plus maze; (ii) less time swimming in a forced-swimming test; and (iii) more time engaged in aggression during a resident-intruder test. No major effect of PPS was found in these general measurements. Under social challenge, we found an interaction between animals' constitution and PPS experience on aggression toward a conspecific, specifically, Low-line rats exposed to PPS displayed abnormal aggression more frequently than other groups. These data indicate that animals selected to have a constitutively high corticosterone response to repeated stress (i.e., impaired adaptation) show enhanced anxiety- and depression-like behaviours at adulthood, as well as altered social behaviour.

Contextual effects on the neural encoding of speech sounds

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Like most sensory brain areas, the human auditory cortex has been shown to be topographically organized. Traditionally, the frequency selectivity of this topographic organization has been characterized. More recently, topographic sensitivities have also been found for spectral and temporal acoustic modulations. This is consistent with the need for a flexible and dynamic auditory processing system, due to our rich and constantly changing auditory environment. Furthermore, at the single cell level it has been shown that auditory receptive fields are responsive to contextual demands. These are the results of animal studies using synthetic stimuli, but it is unknown how these findings translate to humans, and importantly, how they translate to naturalistic contexts. In particular, behaviorally relevant sounds are known to evoke different responses than artificial sounds.

We conducted a 7 Tesla fMRI study in which participants listened to speech sounds while performing two different tasks, one linguistic and one paralinguistic, on the very same stimuli. 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 voxels' receptive fields along three different acoustic dimensions, i.e. frequency, spectral modulations and temporal modulations. We will test for task differences in the voxels' response properties. Specifically, given that successful task performance requires participants to focus on distinctive acoustical features of the sounds, we hypothesize that performance of the two tasks will evoke differential neural encoding of the very same sounds.

Limbic influence on memory: Temporal course of memory encoding and reality filtering

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Previous work showed that immediate picture repetition induced a positive frontal potential at 200-300 ms emanating from the left medial temporal lobe (MTL) (James et al., 2009), presumably due to increased functional connectivity in the theta-band (3-7.5 Hz), and seems to have a memory-stabilizing effect (Thézé et al., submitted) during encoding. Similarly, orbitofrontal reality filtering (ORF) – a process necessary to keep thought and behavior in phase with ongoing reality – induces a positive potential at 200-300 ms over frontal electrodes, which emanates from the orbitofrontal cortex (Schnider, 2013). We investigated how these two processes interact, in particular their temporal sequence. High-density electroencephalograms were recorded from 18 healthy subjects, who performed a continuous recognition task containing stimuli measuring both processes. As expected, both types of stimuli evoked a frontal positivity around 200-300 ms. Finer analysis revealed that the stimuli associated with memory encoding elicited a potential earlier (220 ms) than the ORF stimuli (260 ms). This difference was confirmed with spatio-temporal segmentation, which yielded statistically distinct topographies. Inverse solution localized the signal associated with memory encoding in the MTL and the ORF signal in frontal regions. Overall, our results suggest a model for the limbic system's influences on memory processing: It seems that, immediately after the initiation of a tonic encoding process by the MTL, ORF modulates the memory trace (thought) according to its relation with ongoing reality.

Spatio-temporal brain dynamics underlying attentional bias modifications

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Abnormal attentional biases toward specific elements of the environments have been advanced to characterize and putatively participate in the maintenance of many psychiatric conditions. While behavioral interventions aiming at reducing these biases have been demonstrated to positively influence these pathologies, the neurophysiological mechanisms underlying the modifications of attentional bias (ABM) remain unresolved. We addressed this question by inducing attentional biases toward and away initially neutral stimuli in healthy participants and comparing electrophysiological responses to the cues before vs. after the ABM.

Twenty-four healthy adults performed a modified dot-probe task in which pair of colored shapes (cues) were presented and then replaced by horizontally or vertically aligned double dots (target stimuli). The target stimuli were systematically presented at the same (positive bias) or at the opposite position of a given color (negative bias).

Behaviorally, participants developed either an approach bias toward positive cues or an avoidance bias away from negative cues, but never both together. Electrophysiologically, there was a three-way Group (toward; away) X Session (begin; end) X Stimuli (positive; negative) interaction from 50 to 84 ms post-cue onset driven by decrease in brain activity within left temporo-occipito-parietal regions in response to the cues in (i) positive condition for the “toward” group and in (ii) the negative condition for the “away” group.

Our results show that the development of attentional bias toward or away neutral stimuli influences early attentional processing within the regions of the ventral visual pathway involved in attentional and stimulus saliency processing.

Neurodegenerative Loss of Amygdala Inhibition as an Underlying Cause for Hyper-emotionality: A comparative analysis between patients with Alzheimer's and Urbach Wiethe Disease (A research proposal)

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My PhD project examines hyper-emotionality in patients with Alzheimer's Disease (AD). Hyper-emotionality is frequently observed in AD patients but is poorly understood, though ongoing research in Von Gunten's team has linked these symptoms to problems of insecure attachment.

We aim to gain greater insight into these symptoms by comparing hyper-emotionality in AD patients to hyper-emotionality in a South African population of Urbach Wiethe Disease (UWD) patients. In these patients, UWD has led to bilateral loss (calcification) of the basolateral amygdala (BLA), however detailed fMRI has shown preserved function in the central amygdala (CeA). Fear behaviour, and even hyper-anxiety, are observed in these subjects; likely arising from a loss of inhibitory control of the BLA over the CeA.

Hyper-anxiety in AD patients may similarly stem from a loss of inhibitory control of the BLA (and the prefrontal cortex) over the CeA. We will examine potential hyper-emotionality in AD and UWD patients by means of a variety of experimental affective neuroscience tasks. In addition, these results will be correlated with various characteristics of the participants, including their attachment profile (as measured by the Adult Attachment Interview), their endogenous OT levels (as measured in the blood and cerebrospinal fluid), and a potential loss of BLA control of CeA function (as measured by psychophysical tests and fMRI).

This study aims to better understand the social and emotional functions of the BLA and CeA, with a focus on fear and attachment behaviours and the interaction of these behaviours in AD.

Gene-environment interactions in psychosis: Evaluation of critical time windows for stress during the neurodevelopment in mice with genetic alteration in the glutathione synthesis.

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CHUV

Schizophrenia is a chronic form of psychotic illness affecting about 1% of the world population. Epidemiological studies suggest that both genetic and environmental factors can increase the risk for developing the disorder. In this study we investigate the biochemical and physiological and behavioral outcome in a gene-environment animal model for schizophrenia. Therefore we expose glutathione deficit mice to a 10-day stress protocol during pre-weaning period.
Results: Neither early-life-stress nor glutathione deficit did affect the anxiety
-like behavior in adult mice. Independent on the treatment GCLM KO animals showed an overall increased basal locomotor activity. Sensory motor gating capacity in the prepulse inhibition task was not affected in any of the experimental groups. Mice with redox dysregulation showed reduced spatial working memory ability whereas no deficits in the long-term memory could be observed. Moreover GCLM KO mice exposed to a stress needed more trials to reach the criterion in a water t-maze test. Independent on the treatment mice with glutathione deficit showed cognitive inflexibility and stereotypical behavior when they had to learn a new rule. In parallel to the behavioral testing we collected naïve brains acute after the stress protocol. Stressed animals showed increased levels of 8-oxo-dg (marked for methylated DNA as a result of oxidative stress) and a decrease in WFA-positive cells in the anterior cingulate cortex.

In unbalanced bilinguals, transcranial direct current stimulation of left dorsolateral prefrontal cortex modulates word production similarly in both languages.

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Word-finding abilities depend on the interplay between left perisylvian language-related structures and left-prefrontal control-executive systems, particularly in second languages (L2), where it supports lexical search. While current literature on first language (L1) versus L2 word production suggests that this interaction takes place at onset of lexical access, this assumption lacks empirical support. We investigated the dynamics of the left-prefrontal engagement during language production in late bilingual by applying 1.5mA Anodal transcranial Direct Current Stimulation (A-tDCS) over this area before an ERP picture naming task in their L1 and L2 (late acquisition and intermediate proficiency).

Fifteen participants underwent 20 minutes of 1.5mA (A-tDCS) or Sham (double-blind, counterbalanced stimulation order, intersession delay: one week), and then performed offline the picture naming task in L1 and L2. Behavioral performance and ERP were analyzed with 2x2 ANOVAs with within-subjects factors Language (L1 and L2) and Stimulation (Anodal and Sham).

Behaviorally, there was only a main effect of Language (lower RT and higher correct responses in L1, $p<0.001$). Electrophysiologically, a 2x2 time-frame wise topographic analysis of the ERPs revealed long-lasting main effect of Language, a main effect of Stimulation 150-210 ms post-stimulus onset, and no Language*Stimulation interaction.

Our results suggest that left DLPFC A-tDCS impacted on the conceptual preparation (lexical access) processes during naming, similarly in both L1 and L2. The absence of behaviorally measurable effect of the DLPFC tDCS on naming putatively followed from the weak relative contribution of DLPFC-mediated lexical access processes even in L2.

The neural dynamics underlying different types of perceptual decision-making on affective voices

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UNIGE - Faculté des Sciences

Perceptual decision-making on emotions involves gathering information about the affective state of another person through the senses, cognitively and emotionally processing this information, and the formation of a decision. Certain contexts require different types of decisions on emotions either allowing a free choice according to several categories (unbiased decision) or by urging the perceiver to discriminate a single emotion that is relevant for a specific context (biased decision). In an event-related functional magnetic resonance (fMRI) study, we compared biased and unbiased decisions on auditory emotions (i.e. affective voices), and investigated the patterns of activation and functional connectivity associated with each decision in a network of brain regions that are central to processing affective voices, namely the auditory cortex, the inferior frontal cortex (IFC), and the limbic system (i.e. the amygdala). We first show that unbiased decisions on affective voices recruit bilateral regions in posterior and mid IFC, as well as bilateral amygdala and voice-sensitive areas in the auditory cortex, while biased decisions on affective voices distinctly recruit the right mid IFC. Second, task-induced connectivity revealed strong connections between our regions of interest during unbiased but not biased decision-making on auditory emotions. Third, we show an emotion effect that was present only during unbiased decisions. Together, these data indicate that different types of perceptual decision-making on affective voices have distinct patterns of activation and of functional coupling.

Involvement of the Agmatinergic System in the Depressive-like Phenotype of the *CREB-regulated transcription coactivator 1* Knockout Mouse Model of Depression

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Recent studies have highlighted the involvement of the arginine-decarboxylation product agmatine in depression. Most notably, it has been shown that this compound has antidepressant properties in rodents and that agmatinase (Agmat), the agmatine-degrading enzyme, is upregulated in the brains of mood disorders patients. We have previously shown that mice lacking CREB-regulated transcription coactivator 1 (CRTC1) associate behavioral and molecular depressive-like endophenotypes, as well as blunted responses to classical antidepressants. Here, the molecular basis of the behavioral phenotype of *Crtc1*$^{-/-}$ mice was further examined using microarray gene expression profiling. This analysis revealed an upregulation of Agmat in the cortex of *Crtc1*$^{-/-}$ mice. Quantitative polymerase chain reaction and Western blot analyses confirmed Agmat upregulation in *Crtc1*$^{-/-}$ prefrontal cortex and hippocampus. Immunohistochemical data showed that *Crtc1*$^{-/-}$ mice display more agmatinase-expressing cells than wild-type mice in several brain regions, including the prefrontal cortex and the CA1, CA3 and dentate gyrus regions of the hippocampus. We also observed that agmatinase was most notably expressed in parvalbumin and somatostatin interneurons. At the behavioural level, acute agmatine treatment rapidly (30 min) improved the depressive-like behavior of *Crtc1*$^{-/-}$ mice in the forced swim test, suggesting that exogenous agmatine has a rapid antidepressant effect through the compensation of agmatine deficit due to upregulated Agmat. In wild type mice PFC, agmatine rapidly increased Brain-derived neurotrophic factor (BDNF) protein levels and decreased eukaryotic elongation factor 2 (eEF2) phosphorylation, indicating that agmatine might be a fast–acting antidepressant with NMDA receptor antagonist properties. Collectively, these findings implicate Agmat in the depressive-like phenotype of *Crtc1*$^{-/-}$ mice, refine current understanding of the agmatinergic system in the brain and highlight its putative role in major depression.

Segregation and integration of information in cortico-basal ganglia loops as an in-vivo biomarker of Parkinson's disease

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CHUV

Existing theoretical models fail to integrate hypokinetic and hyperkinetic movement disorders into a unified model of motor dysfunction. Emerging theories hypothesise that the differential clinical phenotypes can be explained by a loss of neuronal specificity in the basal ganglia (BG). The present neuroimaging study investigates in vivo anatomical and functional aspects of information segregation within the cortico-BG circuitry as correlates of dopamine depletion related to the loss of neuronal specificity in Parkinson's disease (PD).

We hypothesise that PD patients will demonstrate abnormal motor somatotopy within cortico-BG circuits that will correlate with their functional impairment and be partially reversed after dopamine substitution, as well as abnormal gradients of cortico-subcortical anatomical connectivity paralleled by specific pattern of BG tissue property changes.

We acquired functional MRI in 20 PD patients tested ON and OFF dopaminergic medication and compared them with 20 healthy controls. The paradigm consisted of an externally paced motor execution task involving movements of the upper and lower limbs. Motor performance was monitored using a customized MR-compatible pneumatic device. Anatomical imaging comprised multi-parameter mapping and diffusion-weighted imaging.

Results showed that parkinsonian BG showed a lack of motor somatotopy that correlated with the degree of motor impairment, which was partially restored with dopamine. Limbic, associative and motor BG territories revealed abnormal connectivity profiles and parallel organization of corticostriatal tracts linking motor somatotopy patterns was lost in PD.

Further analyses will aim to validate the use of this biomarker to detect preclinical stages of PD and monitor therapeutic response to achieve optimal treatment.

Imaging the brain large-scale oxytocin circuits under optogenetic control of hypothalamic neurons

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Oxytocin (OT) is a neuropeptide synthesized in neurons in the paraventricular nucleus (PVN) and supraoptic nucleus (SON) of the hypothalamus. OT is a key mediator of complex emotional and social behaviors. Although the origin (synthesis) of oxytocin as well as the distribution of its receptors in the brain have been described, we have only started to disentangle by which mechanism (i.e. diffusion and/or axonal release) OT from the hypothalamus penetrates the different limbic regions and reaches its receptors in sub-regions of the amygdala that are important for fear and social cognition.
In order to decipher the OT circuitry we choose to work on the olfactory system. Our approach is to induce the activation of the specific olfaction subsystem through the use of fearful odorants. The involvement of OT in this process will be assessed by optogenetic activation of OT neurons in the PVN. Finally, behavioral and MRI studies will allow to observe the effects of this activation.
Ongoing preliminary studies are focusing on the validation of the innate fear-induction protocol in rats. Next step will be to determine exactly which part of the amygdala is activated by olfactory neuron projection in order to characterize the specific underlying oxytocin circuitry involved in this system. The aim of this study is to improve our understanding of the large-scale neurocircuits modulated by intrinsic release of OT from the hypothalamus and its importance for psychiatric pathologies.

Tracking down the syllabic rhythm in the brain: an EEG study.

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The presence of variations in speech rate is one of the many distortions of the speech signal that the human speech perception system has to deal with in everyday life situations. Previous studies (Peelle, Gross & Davis, 2013; Doelling, Arnal, Ghitza & Poeppel, 2014) using Magnetoencephalography (MEG) suggest that slow brain oscillations, in the same frequency range as the syllabic rhythm, may play a role in speech comprehension by tracking syllable onsets. In this study we employed time-compressed speech to manipulate the syllabic rhythm and investigate whether brain oscillations adapt to these differences in speed and whether this speech-bran coherence changes as a function of speech intelligibility. Behavioural and Electroencephalography (EEG) data were collected from 17 volunteers while they were listening to sentences compressed at different rates. In line with previous studies, behavioural results revealed that the more compressed the acoustic signal the more difficult it is to comprehend it. We computed the cross-spectral density between the acoustic signal and the EEG measured at each electrode. Higher values were obtained around the syllabic rhythm frequency for each compression rate. Current analyses are focusing on reconstructing the underlying brain sources that track the syllabic rhythm and investigate how phase locking in auditory regions varies as a function of speech intelligibility. These results replicate and extend previous findings by using a different technique to investigate time-compressed speech comprehension and cerebro-acoustic coherence.

The impact of language opacity on reading strategies in unbalanced bilinguals: an eye movement study

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Different eye-movement patterns have been observed when reading transparent (simple grapheme/phoneme conversions) or opaque languages (complex grapheme/phoneme conversions). We recently showed that early and proficiency balanced bilingual individuals presented a local reading strategy when reading in their transparent (German) compared to their opaque language (French), supporting the influence of language opacity on reading strategies. The present work aims to test whether corresponding effects are manifested in bilinguals with a low proficiency level in their second language (L2). Accordingly, we recorded eye movements while two groups of unbalanced bilinguals with either French or German as first language (L1) read aloud isolated French and German words and pseudo-words. Since a transparent reading strategy is local and serial (first fixation location (FFL) close to the beginning of the stimuli associated to a high number of fixations per stimuli) and the level of bilinguals' L2 is low, the impact of language opacity should be modulated by bilinguals' L1. We therefore predicted a global reading strategy when reading in French in bilinguals with French as L1 (FFL close to the middle of the stimuli with fewer fixations per stimuli), and a transparent reading strategy in bilinguals with German as L1 when reading in German. In addition, participants should preferentially require a local and serial strategy when reading in their L2. Our results confirmed these hypotheses and suggest that global word processing is only achieved by unbalanced bilinguals with an opaque L1 when reading in an opaque context.

Relationships between autism and schizophrenia spectra: Insights from autistic and schizotypy personality traits, pareidolia-proneness, and gaze processing.

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UNIL-LERB

Schizophrenia (SSD) and autism (ASD) spectrum disorders share clinical features, although they are considered distinct entities. Psychometric studies using self-report schizotypy and autistic trait questionnaires support shared, but also opposing features. In two studies, we validated such psychometric tools in French (schizotypy: sO-LIFE, autistic traits: AQ) and replicated the psychometric relationships in a French-speaking sample (Sierro et al., in press; submitted). In two additional studies, we tested whether these shared and opposing relationships emerge behaviourally, namely in social functioning tasks. In one study, we assessed participants' proneness to see faces in noise (pareidolia) and in another participants' gaze processing (gaze discrimination, attentional gaze cuing). We expected that both stronger pareidolia-proneness and superior gaze processing would go along with enhanced positive schizotypy and reduced autistic mentalism traits. For pareidolia-proneness, we only found that face processing was impaired with increasing positive schizotypy and enhanced with decreasing autistic mentalizing deficits. For gaze processing, increasing autistic mentalizing deficits associated with decreasing gaze sensitivity and increasing positive schizotypy with increased gaze sensitivity. To conclude, our results show psychometric stability of the validated schizotypy and autistic trait questionnaires for French-speaking samples, including their interrelationships. The interrelationships emerged partially, but not entirely for the social cognitive tasks. We propose that the theoretical idea for pareidolia-proneness was promising, but improved paradigms might reveal more clear-cut results. Gaze processing, too, was promising. We suggest further improvements for future studies so to better understand what might be common or distinct (if not diametrically different) in ASD and SSD.

Exogenous orientation of the visual attention by trigeminal stimulation of nostrils

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UNIGE - Other

The survival of many individuals and of many species is made by smell. It can allow food selection, hygiene appraisal, danger warning and the research of a suitable partner. Olfaction and the trigeminal nerve are the two main sensory systems that enable human beings to detect volatile molecules. Actually, almost all volatile compounds stimulate both sensory systems, since odors are usually both smelled and felt by the nose. However, only the trigeminal component of the odor enable human to differentiate a left nostril stimulation to a right nostril stimulation. During the last decade, studies have shown that there is a common pool of attentional resources for the processing of auditory, visual, tactile and olfactory stimuli. It is therefore likely that the lateralised information perceived by the trigeminal system is being automatically used by human to make appropriate choices in the noisy scene of everyday life and to influence the visual selective attention in determining which stimuli enter awareness and which do not. However, the exogenous spatial orientation of the visual attention by an odor, to our knowledge, has never been tested.

This research aims at better understanding if and how trigeminal stimulation influences spatial attention. To do so, CO2, a gaz considered as a pure trigeminal stimulant was used in a variant of the “cueing paradigm”. Participants were required to detect as fast and as accurately as possible a target following a lateralized cue induced by a CO2 stimulation. Preliminary results show an orientation of the visual attention on the side of the CO2 stimulation.

Does Heat Smell Bad?
Cross-modal expectancy effects between Pain and Disgust

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UNIGE - Faculté des Sciences

When we form expectations regarding future events, we become more sensitive in detecting them. For instance, increased pain sensitivity occurs when the intensity of an upcoming stimulus could be predicted. This effect is knowingly mediated by the anterior insula. However, it is still unknown whether expectations of pain trigger a representation of sensory-specific information of the upcoming event or of its aversive-affective ("unpleasant") consequences, potentially common with other unpleasant situations such as disgust. We used fMRI and compared for the first time expectancy effects of pain and disgust by using different, but equally unpleasant, nociceptive (thermal) and olfactory stimulations. Cues predictive of the unpleasantness (high/low) and the modality (pain/disgust) of upcoming events were shown to participants, who subsequently rated the subjective unpleasantness associated with thermal/olfactory stimuli on a Likert scale. Reminiscently of earlier studies, we found that the same thermal stimuli were perceived as more unpleasant if preceded by cues threatening about high (as opposed to low) pain. A similar expectancy effect was also found in the domain of disgust. Critically, expectancy effects were observed with the inconsistent trials, in which thermal stimuli were preceded by high-disgust cues, or olfactory stimuli were preceded by high-pain cues. However, the effects were stronger in the consistent rather than inconsistent settings. Taken together, our results suggest that expectation of an unpleasant event elicits representations of both its modality-specific properties and its aversive consequences. Analysis of the brain signal associated with this task shed light on the neural substrate underlying these representations.

Neuroplastic changes associated with functional recovery in amblyopia - anatomical and behavioural characteristics of training-dependent brain plasticity

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Recent developments in the treatment of amblyopia suggest that by targeting deficient binocular summation and suppression mechanisms amblyopic eye function can be improved past the critical period of development into adolescence and adulthood. In this study we intend to train amblyopic subjects and matched controls on a dichoptic visual task while tracking functional and microstructural brain changes with clinical behavioural and longitudinal neuroimaging data. The neurobiological mechanisms underlying the reorganisation of the mature human brain associated with training or recovery of lost function are largely unknown. To address the limitations of previous studies we apply a multimodal neuroimaging approach combining quatitative measures of tissue microstructure and receptive field properties. This interdisciplinary project offers the unparalleled opportunity to make a significant contribution to our understanding of brain plasticity with major clinical relevance in rehabilitation and restoration after brain function loss.

Impact of electronic device use on sleep in adolescents

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Sleep plays a critical role for cognitive and affective functions. Recent research suggests that experience-dependent synaptic changes do not only occur during adult sleep but also serve brain maturation in childhood and adolescence. Based on these observations, we hypothesized that the expansion of electronic media use might cause a state of chronic sleep deprivation in adolescents. Specifically, increased arousal and the blue-light emitted by the screens would delay sleep onset.

We thus assessed the use of electronic devices and measured the sleep habits of 413 Swiss adolescents between 12 and 21 years old using actigraphy, daily diary, and melatonin profile. Second, we evaluated the impact of a simple educative recommendation on sleep, by asking adolescents to stop using electronic devices after 9pm (N=276).

Preliminary results revealed insufficient sleep in adolescents, with about one hour less than recommended (9h), particularly in older participants. Adolescents also spent 1h30 using media after 9pm. Social network activities was the most used media and significantly delayed sleep onset ($r=0.37$; $p<0.001$) while homework do not have an impact on bed time ($r=0.02$; $p=0.52$). For those who stopped using media after 9pm, media use decreased by 53min (± 51min) and total sleep time increased by 15min (± 38min). Reduction of media use in the evening significantly correlated with earlier sleep onset ($r=0.38$; $p<0.001$).

These findings demonstrate that the emergence of new technologies profoundly modifies sleep habits and induces a chronic sleep deprivation in adolescents. A simple recommendation (no media use after 9pm) can improve their sleep.

Peripheral Administration Of Lactate Produces Antidepressant-Like Effects

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Growing evidence indicate that astrocytes are involved in the pathophysiology and treatment of depression. With respect to energy metabolism, astrocytes respond to glutamatergic activation by increasing the rate of glucose utilization and the release of lactate. In relation to depression, studies in cultured astrocytes have revealed that SSRI antidepressants stimulate glycogenolysis, glycolysis and lactate release. In addition to its role as a neuronal energy substrate, recent data from our laboratory indicate that lactate increases the expression of plasticity-related genes including BDNF, a neurotrophic factor involved in major depression and antidepressant treatment. Together, these data suggest that, by increasing the expression of plasticity-related genes, and particularly BDNF, lactate may produce antidepressant-like effects.

The aim of this study was to investigate the effects of peripheral administration of L-lactate on depressive-like behavior. Using a L-lactate selective biosensor inserted within the mouse hippocampus, we first showed that intraperitoneal injection of L-lactate, that raised blood lactate concentration by 2-3 fold, induced a long-lasting increase in extracellular lactate concentration. We next examined the effects of peripheral L-lactate administration on depressive-like behavior. Acute intraperitoneal injection of L-lactate reduced immobility in the forced swim test. Further investigation of the antidepressant effects of L-Lactate showed that daily injection of L-lactate for three weeks decreased, to a similar extent as desipramine, the immobility time in both the repeated open-space forced swim test and corticosterone-induced depression model.

In conclusion, our data indicate that peripheral administration of L-lactate produces acute and chronic antidepressant-like effects.

Sensory substitution: Does an orientation discrimination training of simple 'soundscape' objects transfer to more complex stimuli?

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CHUV

Human beings rely heavily on their sense of vision to perceive forms and identify objects in the environment. When visual abilities are degraded or even absent, auditory cues can help object recognition and orientation. In recent years, sensory-substitution devices (SSD) have been developed to help blind individuals navigating by the help of auditory, but also somatosensory cues. A recently developed vision-to-audition substitution device named EyeMusic has been recently developed in the lab of Amir Amedi at the Hebrew University of Jerusalem. The algorithm implemented in the device transform visual forms ("landscapes") into so-called "soundscapes" whereby the height of an image is reflected by the pitch of a sound, whereas the location of objects from left to right is coded by sound latency.
Based on the functioning of the device, we conducted a first study in healthy seeing individuals to investigate whether the training of orientation discrimination on simpler objects increases the discrimination of more complex objects.

Thanks to the support of the Jean Falk-Vairant foundation, I was able to visit the EyeMusic lab in Jerusalem to train on the EyeMusic algorithm in order to conduct extensive research on its impact on substitution-induced changes in behavior and brain plasticity in my home lab.

A time and a region-specific role of astrocytic lactate in the formation and maintenance of positive affective 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. We recently demonstrated that disrupting glycogenolysis in the basolateral amygdala (BLA) impaired the acquisition and maintenance of positive affective memories associated with cocaine-associated cues.Rats that received intra-BLA infusions of the inhibitor of glycogen phosphorylase, 1,4-dideoxy-1,4-imino-D-arabinitol (DAB 300 pmol/side) did not acquire a cocaine-induced conditioned place preference (CPP). A double DAB infusion (15 minutes prior and 5 hours after contextual re-exposure) abolished the cocaine attractiveness already established 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) signalling pathway. We then tried to replicate our observations by targeting the prefrontal cortex (PFC), but rats continued to exhibit a strong preference for the cocaine compartment. However, recent evidence established that consolidation of drug reward memories depended on successive phases (Gholizadeh et al, 2013), with the BLA involved in the early phase and the PFC possibly involved in the late phase of memory consolidation. Rats were injected with DAB (480 pmol) into the PFC fifteen minutes and twelve hours after the contextual re-exposure. In contrast to rats injected with DAB 15 min/5h, those treated 15 min/12h 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.

Computational Neuroscience

Creation and validation of new tissue priors for automated classification of subcortical brain structures

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Despite the constant improvement of algorithms for automated brain tissue classification using T1-weighted (T1w) magnetic resonance images (MRI) data, the problem of accurate delineation of subcortical structures remains unresolved. The main challenges are the low grey-white matter contrast in these iron rich areas and the lack of adequate priors for basal ganglia and thalamus. Most recent attempts [1],[2] to address this issue were hampered by the few subjects included and their narrow age range, which does not allow to account for the age-related tissue contrast changes in T1w MRI protocols. Aiming to improve the anatomical plausibility of automated brain tissue classification, we created new tissue probability maps for the subcortical structures. Supported by atlas-derived information, raters performed manual segmentation in a large cohort of healthy subjects using magnetization transfer saturation and R2* maps, which feature optimal tissue contrast for these areas. After assessment of inter-rater variability, the new tissue probability maps were implemented and tested in the framework of voxel-based morphometry. The new probability maps demonstrated an increased accuracy for grey matter voxels in all subcortical areas, compared to classification performance of current tissue priors. We provide evidence for improved delineation of basal ganglia and thalamus, which overcome the age-related bias in accurate segmentation of iron rich subcortical regions. The new tissue priors, allowing robust detection of basal ganglia and thalamus, have the potential to enhance the sensitivity of voxel-based morphometry in healthy brain and disease.

[1] Ahsan et al., NeuroImage, 2007
[2] Keuken et al., NeuroImage, 2014

Estimation of Alzheimer's disease progression in-vivo with MRI-based measures of atrophy

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CHUV

Introduction
Clinical diagnosis of Alzheimer's disease criteria are focusing on memory loss as the central emerging characteristic of Alzheimer's disease (AD). Current AD diagnostic criteria lack the power to reveal pathological change in the brain, especially neurofibrillary tangles deposition in Braak stages. MRI-based measures of atrophy map accurately with neurofibrillary tangles aggregation during Braak stages. In this project, we propose to estimate Alzheimer's disease status based on grey matter atrophy levels.
We first aim to test the association between the estimated stages and clinical diagnosis and the relation with longitudinal diagnosis conversion among the cognitive controls. Our second goal is to reveal, in various stages, the atrophied anatomical regions and their discrimination parameters.

Method
We collected 710 T1 weighted MR images from ADNI study. There are 223 controls, 386 mild cognitive impairments and 101 AD. The extracted volume from grey matter regions were used as observed item scores. We used continuous-response model (CRM) to estimate the latent trait for all subjects. The model was estimated with maximum likelihood algorithm. We simulated data with factor model to test the performance of this algorithm. Survival analysis was performed to test the association between the estimated disease stages with longitudinal diagnosis conversion. Item characteristic function was used to access the structural parameters of the regions.

Results
Based on the simulated data, the underlying latent traits from observed variables can be estimated. The estimated disease stages associate with clinical diagnosis by using two sample T-test.

Conclusion
CRM can be used to estimate the underlying disease stages.

Speech Processing by Neural Oscillations in a Predictive Coding Context

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UNIGE - Campus Biotech

Cortical oscillations are involved in speech recognition. A recent neurocomputational model from our laboratory establishes that coupled theta and gamma neural oscillators can segment speech into syllable units and organize gamma-range spiking intro a decipherable neural code (Hyafil et al., e-life, in revision). This model, however, lacks top-down control, which is determinant in on-line speech recognition (Gagnepain et al. 2012), presumably through beta oscillations (Fontolan et al. 2014, Bastos et al. 2014, van Kerkoerle et al. 2014). Here we set out to understand how theta, beta and gamma oscillations interact in speech processing. We address this question using a predictive coding model of auditory cortical operations involving a hierarchy of timescales. The top level is the slowest one- it encodes words through sequentially activated units representing syllables that make a stable heteroclinic channel (SHC). Each syllable unit evokes another SHC with faster units nested in it, which track the sensory input. We compared this model with an existing 2-level speech recognition model (Yildiz et al. 2013) on a multi-syllable word recognition task. The two models performed equally well on whole words, but the three-level "timed" model, with its implicit syllabic rhythm (theta), gave better results because it was able to identify word parts (syllables), thereby reducing the amount of data to be evaluated at once. Our ongoing work tests the constraints imposed by beta modulations of top-down predictions in speech processing. Top-down beta possibly reflects the rhythm at which central brain processes integrate information and transmit predictions to the periphery.

Characterizing brain tissue classification using non-enhanced computed tomography

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Non-enhanced Computed Tomography (NCT), as a primary neuroimaging tool in the prognosis of stroke patients, has become a clinical fundamental technique for diagnosis of acute stroke. Several studies have demonstrated the raising interest in studying clinical NCT images using spatial normalization for group studies. However, spatial normalization often uses tissue probability template which comes from Magnetic Resonance Imaging (MRI). There is no clear evidence of how MRI tissue probability template affects NCT-based Grey Matter Volume (GMV) estimation. We hypothesized that differences in GMV between NCT and MRI would be mainly localized in subcortical brain structures. To that end, we compared volume estimation at global and voxel level and derived new tissue prior maps from normalized smoothed NCT images. We showed significant GMV differences between NCT and MRI mainly located in the basal ganglia. Our findings provide strong evidence of higher signal in basal ganglia when using the NCT tissue probability template. Overall, our study illustrates how such template not only enables a better GMV estimation of subcortical areas but also provides a reliable framework for automated lesion detection using clinical stroke NCT data.

Development

A fraction of cortical interneurons expressing the ionotropic serotonin receptor 3A are derived from the preoptic area.

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UNIGE - CMU

Cortical interneurons (INs) constitute a highly diverse population of neurons that are key regulators of cortical microcircuit function. During development, specific subclasses of cortical INs originate from distinct subpallial microdomains. The vast majority of INs derive from progenitors located in the medial and caudal ganglionic eminences (MGE and CGE, respectively), whereas about 10% of INs derive from the preoptic area (POA). CGE-derived interneurons, in contrast to MGE-derived INs, specifically express the ionotropic serotonin receptor 3A (5-HT3AR). Here, we aimed to determine whether POA-derived INs express the 5-HT3AR and investigate their molecular and electrophysiological properties. In vivo lineage-tracing experiments using Nkx5.1-cre mice revealed that about 15% of 5-HT3AR cortical INs originate from a restricted POA region located ventrally to the anterior commissure. POA-derived cortical 5-HT3AR+ INs expressed neuropetide Y and/or reelin, the transcription factors PROX1, NR2F2 and SP8. We are currently investigating the electrophysiological properties of POA-derived INs. Taken together, these results indicate that 5-HT3AR+ INs derived from the POA display distinct molecular, morphological and electrophysiological properties, which make them more similar to CGE then MGE-derived INs.

Studying the impact of the 5-HT3AR and early-life stress on affective circuits and psychiatric-relevant behaviors.

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Abstract: Exposure to early-life stress (ELS) is known to increase risk to psychopathologies such as depression and anxiety disorders later in life. In humans serotonin-related genes such as the serotonin receptor 3 (5-HT3AR) interacts with ELS to increase risk to stress-related disorders. Furthermore, recent data from the lab indicates that childhood maltreatment significantly impacts the methylation status of the promoter region of the human 5-HT3AR in an allele-specific manner. Interestingly the 5-HT3AR is specifically expressed in a subset of cortical interneurons (INs) derived from the caudal ganglionic eminence (CGE). Recent work form our lab has shown that the 5-HT3AR controls early steps of cortical circuit assembly such as the migration and positioning of specific subtypes of cortical INs. Here we aimed to study the interactions between ELS and the 5-HT3AR at a behavioral and functional level using 5-Ht3ar-ko mice. To do this a perinatal stress protocol was performed in control and 5-Ht3ar-ko mice and behavioral testing was done in adulthood. Behavioral data indicate that ELS interacts with the 5-Ht3ar to modulate social behaviors and that 5-Ht3ar-ko mice display anxiolytic behaviors. RNA- and MBD-sequencing of mPFC and ventral Hippocampus (vHPC) is underway in order to identify genes that are induced by ELS and are targets of 5-Ht3ar. Ongoing work is aimed at studying the role of the 5-HTR3A and serotonin modulation on functional circuits controlling affective behaviors using local field potential recordings. To do this we propose to use 5ht3ar-Cre or SERT-Cre mice in combination with a DREADD approach to manipulate these functional circuits in a cell-specific manner.

Evolution of novel glomerular targeting specificities in drosophila olfactory sensory neurons.

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UNIL-CIG

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 different, but adjacent, glomeruli. Here we aim at unraveling the molecular mechanisms underlying these subtle targeting differences to give rise to these three distinct olfactory circuits. To identify molecules involved in IR75a, IR75b and IR75c neuron axon targeting, we have 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 different receptor genes. Here we present preliminary results from these methods and show that we can identify putative axon guidance molecules responsible for the differential wiring of IR75a, IR75b and IR75c expressing neurons. We are currently analyzing the most promising candidates by RNAi and classical loss-of-function genetic analysis to confirm their role in circuit wiring. Our results will shed light into the molecular mechanisms underlying the assembly and evolution of neural circuits.

Investigating the role of KCC2 in cortical microcircuit formation

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UNIGE - CMU

The neuron-specific K+/Cl- cotransporter KCC2 plays a major role in driving GABAA receptor-mediated synaptic inhibition in the mature central nervous system. Early observations suggest that developmental upregulation of KCC2 in the neocortex occurs during the early postnatal period and, concomitantly, drives the functional transition of GABAergic neurotransmission from excitatory toward inhibitory modalities. Recent data, however, indicate that KCC2 might also be expressed in distinct brain regions at earlier developmental stages and, importantly, could play a morphogenic role during brain maturation. The goal of my project is to further extend this hypothesis. To investigate the expression of KCC2 in the developing brain, we performed a series of in situ hybridization studies in the mouse brain between embryonic day (E) 14.5 and 17.5 as well as in the early postnatal period. These investigations revealed KCC2 mRNAs expression as early as E14.5 in several structures of the ventral forebrain. Immunohistochemistry using an antibody against the KCC2 protein confirmed these observations. At E17.5, KCC2 expression was also enriched in the cortical plate. Further analysis, using transgenic mice lines where medial ganglionic eminence-derived GABAergic neurons are fluorescently labeled, revealed that KCC2 is colocalized with a subset of those migrating interneurons. To further explore whether KCC2 might play a role in the migration of these neurons, we are planning to perform a series of experiments to constitutively down-regulate KCC2 in distinct interneuron populations and examine how these genetic manipulations affect the development of these cells.

Wnt signaling regulates multipolar-to-bipolar transition of migrating neurons in the cerebral cortex

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Cortical layers are generated by precisely coordinated cell migration events and the mammalian cortex is particularly susceptible to disorders of migration. Understanding the mechanisms and regulation of migratory events is therefore crucial to understand how alterations in this process might contribute to neurodevelopmental disorders. Here we report that Wnt canonical as well as non-canonical signaling are active in pyramidal precursors during radial migration. We demonstrate using constitutive and conditional genetic strategies that transient down-regulation of canonical Wnt/ß-catenin signaling during the multipolar stage plays a critical permissive role for polarizing and orienting cells for radial migration. In addition, we show that reduced canonical Wnt signaling is initiated cell autonomously by time-dependent expression of Wnt5A and activation of non-canonical signaling. We identified ephrin-B1 as canonical Wnt signaling-regulated target in controlling the multipolar to bipolar switch. These findings highlight the critical role of Wnt signaling activity in neuronal positioning during cortical development.

Role of microRNA 137 in cortical circuit formation

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UNIGE - Faculté des Sciences

MicroRNAs are critical to neurodevelopment and adult neuronal processes by modulating the expression of multiple genes within biological networks. In a recent whole-genome methylome screen performed on patients with severe borderline personality disorder, we have found that early-life adversity significantly increased the methylation status of a CpG site (cg14035771) upstream of MIR-137 (Prados et al. 2015). In addition several genome-wide association studies (GWAS) indicate that SNPs in the MIR-137 locus are associated to increased risk for psychiatric disorders including schizophrenia and autism spectrum disorders. Mechanisms that link MIR-137 to these phenotypes are unknown, but could be related to the proper formation and assembly of cortical circuits. Interestingly and in an evolutionary perspective, MIR-137 appears to be related with cortex folding of gyrencephalic mammal species and is expressed at only very low levels in the mouse developing cortex. A microarray performed on the postnatal cortex of the ferret at P2 revealed increased expression of MIR-137 in the prospective splenial gyrus compared to the prospective lateral sulcus in three germinal layers of the visual cortex (VZ, ISVZ, and OSVZ). Based on these results, we aimed to investigate the role of MIR-137 in the migration and differentiation of upper-layer pyramidal neurons (PNs) by over-expressing MIR-137 in the developing mouse cortex. Preliminary results of in utero electroporation experiments, targeting E14.5 dorsal pallial precursors, indicated that MIR-137 overexpression increased the migratory speed of PNs and led to the premature positioning of PNs in the cortical plate. Current studies are designed to investigate the mechanisms that mediate this phenotype.

The role of DiGeorge Critical Region 2 gene in cortical circuit formation

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UNIGE - CMU

Using in vivo cell-type specific manipulation of pyramidal neurons progenitors, we aim to investigate the role of DiGeorge Critical Region 2 (DGCR2) on cortical circuit formation, a critical process involved in schizophrenia vulnerability. DGCR2 is located in the 22q11.2 locus, whose deletion is one of the highest known risk factor for schizophrenia (SZ), and codes for a transmembrane protein expressed during cortical development. Interestingly, exome sequencing revealed a de novo DGCR2 mutation in an idiopathic schizophrenic patient. Here we aimed to investigate the role of DGCR2 in early steps of cortical circuit formation using in utero electroporation targeted to pyramidal neurons (PNs). Knock-down 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. DGCR2-shRNA-induced mispositioning could be fully rescued by overexpressing the human (h)DGCR2, which is not targeted by the mDGCR2-shRNA. In contrast, (h)DGCR2 containing the de novo mutation was not able to fully rescue the DGCR2-shRNA-induced mispositioning phenotype, indicating a functional role for this mutation. 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. These studies will allow us to understand the role of the SZ-risk gene DGCR2 on cortical circuit assembly.

Becoming a new neuron in the cerebral cortex

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UNIGE - CMU

The cerebral cortex is composed of distinct types of neurons that assemble to form specific circuits during development. Over recent years, much progress has been made in understanding the type-specific gene expression of these neurons at relatively late stages of differentiation, once they have reached the cortex. However, their early postmitotic, pre-circuit biology remains unexplored. To investigate this question, we developed a novel “Flashtag” technology, which allows in vivo labeling of precise time- and phase-locked cohorts of cells at the ventricular zone. This high temporal resolution approach permits fluorescent tagging of single nascent neurons and their progenitor right from the time of mitotic division. Using this strategy, we were able to longitudinally characterize cell type-specific primordial transcriptional activity as it was unfolding during the crucial first 12 hours post cytokinesis. Our results provide exciting first insights into the type-specific native genetic programs that direct the initial steps of neuronal differentiation. For example, we observe that transition between mitotic and post-mitotic cells is not a discrete transcriptional event, but instead occurs gradually during differentiation. Together, these findings shed new light on the transcriptional dynamics underlying cellular diversity andprovide a novel vista on postmitotic differentiation and plasticity in the developing mammalian neocortex.

Integration of grafted neuronal progenitors into the postnatal cerebral cortex.

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UNIGE - CMU

Neuronal death is the key event in the pathogenesis of many neurological disorders. Since the postnatal cortex has a limited regenerative capacity, transplantation of neural progenitor cells may represent a potential way to compensate neuronal loss. However, little is known about integration of grafted cells into the host circuits. To address this issue we utilized a highly efficient diphtheria toxin/diphtheria toxin receptor based model to induce synchronized apoptotic death of the layer II neurons in the rat somatosensory cortex at P16 (the period of activity-dependent plasticity). Transplantation of embryonic progenitors was carried 4 days after the lesion that was followed by the analysis of grafts at days 7, 14 and 30 after transplantation. Our results indicate long-term survival and good tissue integration of transplanted cells that typically remain in cluster. Donor cell clusters send out numerous outgrowth to the host tissue and receive innervation from the cortex and thalamus. Transplanted neurons in cluster are engaged in synaptically interconnected networks (developed dendritic tree, protrusions formation, axonal projections, synaptic contacts with the host layer IV neurons). The lesion environment promotes maturation of transplanted progenitors enhancing the complexity of their dendritic tree and number of dendritic protrusions. Moreover, early transplantation after the lesion as well as intrinsic stimulation of grafted cells improves their integration into the host network. The model provides new possibilities for exploring the integration of transplanted cells into preexisting network following injury.

Olfactory perception in newborns using fMRI

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The olfactory system is one of the first sensory systems to be functional during fetal life and has a high behavioral importance following birth. Behavioral and NIRS studies have demonstrated that neonates are able to detect and differentiate a large number of different odors, but underlying neuroanatomical substrates are poorly understood. In this fMRI study, we aimed to investigate the neural pathways activated in newborns following artificial olfactory and trigeminal odorants stimulation.

Two runs of functional MRI were acquired during odorants stimulation in 28 full-term newborns during first week of life in a 3T MRI without any sedation. Three odorants: cabbage like (olfactory), banana like (bimodal:olfactory>trigeminal) and eucalyptol (bimodal:trigeminal>olfactory), were delivered using a four way odorant delivery system. Each odorant was delivered independently during 20 seconds in a pseudo-randomized order and separated with a neutral odour (water).

At the group level, we observed a significant activation of olfactory areas to odorant stimulation ($p<0.005$, 10 voxels extent threshold), especially in bilateral piriform cortex following olfactory odorants. Habituation analysis showed that the habituation effect is not observed in the bloc design into the activated olfactory areas.

Functional activation of main olfactory areas can be localized with fMRI in the newborn brain following artificial odorant stimulation. Newborns respond to different kind of new artificial olfactory and trigeminal odorants that have no biological relevance. This study shows that the olfactory cortex of newborn infants is highly functional soon after birth and that the habituation effect is less present than in adults.

Functional connectivity in the salience network differs between preterm at term equivalent age and fullterm newborns.

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Because it only needs the subject to be at rest, Resting State fMRI (RS-fMRI) is a promising technique to investigate functional connectivity development in newborns. RS-fMRI is related to the underlying structural connectivity and modulated by brain development. The salience network, consisting of anterior cingulated cortex (ACC) and insula, facilitates the detection of relevant internal or environmental stimulus and assists target brain regions in the generation of appropriate behavioral responses. Furthermore, its connectivity seems to be influenced by early life events: adults with childhood emotional stress as well as adults born prematurely have been shown to have an altered salience functional connectivity.

Thus, the aim of this study is to investigate salience functional connectivity in full-term and preterm at term equivalent age (TEA) newborns and to assess how premature exposure to extra-uterine environment impact on its early development.

We acquired 8 minutes of RS-fMRI (Siemens 3T scanner) without any sedation in 25 full-term and 25 preterm at TEA infants. Data from both groups have been decomposed into 16 relevant components in a single group-level independent component analysis (ICA).

We found networks consistent with those previously described in infants and in adults. Furthermore, we show a decreased connectivity between salience network and three other networks: superior frontal, orbitofrontal and auditory networks in preterm at TEA newborns. Salience connectivity has been shown to be altered in various neuropsychiatric disorders, such as autism, attention disorders and anxiety. Thus, decreased salience connectivity in preterm children may be related to their increased risk for emotional and behavioral disorders.

Molecular and Cellular Neuroscience

Structural analysis of RGL stem cells and their Niche in the adult hippocampus

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Hippocampal adult neurogenesis is tightly regulated by the stem cell's highly specialized microenvironment, called the neurogenic niche, which can potentially include every brain cell type: neurons, microglia, endothelial cells, astrocytes and oligodendrocytes. Understanding the interactions between adult neural stem cells and their niche is crucial for a full understanding of the regulation and function of the neurogenic niche.
Here, we examined the morphological characteristics of adult neural stem cells and the nature of their interactions with the neurogenic niche.

RNAi FOR HUNTINGTON'S DISEASE: MAXIMIZING THERAPEUTIC BENEFIT WITH RETROGRADE TRANSPORT AND NEURONAL/ASTROCYTIC TRANSDUCTION OF VIRAL VECTORS

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CHUV

Huntington's disease (HD) is a neurodegenerative disease characterized by motor, cognitive and psychiatric dysfunctions with no curative treatment available. This monogenic disease is due to an extended CAG repeat coding for glutamine in the IT15 gene. The striatum is the first structure to degenerate in HD but others structures are affected as well. In addition, neuronal as well as glial cells contribute to the pathology. One promising strategy to treat this pathology is to deliver small hairpin RNA (shRNA) to silence the mRNA coding for mutant huntingtin (HTT) protein.
We propose to take advantage of the neuronal circuitry to reach the affected structures. Most of them project to the striatum and could be reached by retrograde transport. To transduce both neurons and astrocytes and further maximize therapeutic benefit, we have tested the ubiquitous Polymerase III H1 promoter.
We first evaluate the retrograde transport properties of different AAV serotypes (AAV-2/5, -2/6, -2/9 and -2/10) and of a new VSV-Rabies pseudotyped lentiviral vector (LV) expressing the green fluorescent protein (GFP) in adult mice. Our results showed that all vectors underwent retrograde transport in thalamus, substancia nigra pars compacta and globus pallidus revealed by GFP-positive cell bodies. However, only LV efficiently transduced cortical neurons. Based on these data, the VSV-Rabies pseudotyped LV-H1-shGFP was selected to investigate cell-type specific silencing in transgenic mice expressing GFP in GABAergic neurons of the indirect pathway (Drd2-GFP mice) or astrocytes (GLT1-GFP mice). We demonstrate efficient GFP silencing in striatal neurons and astrocytes. Silencing in projecting area is currently under investigation.

Hippocampal somatostatin interneurons control the size of neuronal memory ensembles

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UNIGE - NEUFO

Hippocampal neurons activated during encoding drive the recall of contextual fear memory. Little is known about how such ensembles emerge during acquisition and eventually form the cellular engram. Manipulating the activity of granule cells (GC) of the dentate gyrus (DG), we reveal a mechanism of lateral inhibition that modulates the size of the cellular engram. GC engage somatostatin positive interneurons that inhibit the dendrites of surrounding GC. Our findings reveal a microcircuit within the DG that controls the size to the cellular engram and the stability of contextual fear memory.

Modulation of molecular substrates of thalamic rhythmogenesis through synaptic NMDA receptors

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UNIL-DNF

Thalamic circuits are considered reliable and stereotypic pacemakers for sleep rhythmogenesis. Yet, it is well known that sleep oscillations vary in intensity, locally and globally in the brain, due to circadian, homeostatic and use-dependent regulatory influences. Which are the activity-dependent mechanisms within corticothalamic circuits that could drive such variability? In the nucleus Reticularis thalami (nRt), neuronal activity during sleep is governed by low-threshold spiking through CaV3-type calcium channels. In addition, cortico-nRt synapses express GluN2C-containing NMDA receptors (NMDARs) that contribute to thalamic excitability and have been linked to the emergence of pathophysiological oscillations. We explored synaptically mediated modulation of nRt discharge using selective optogenetic activation of cortical layer VI afferents in slices from NtsR1-CreXChR2floxed mice. We found that repetitive photostimulation of cortical inputs (10Hz trains) induced a long-lasting increase of postsynaptic potentials in nRt cells (29±9%, n=7, $p<0.05$), which was sensitive to the GluN2C-preferring blocker PPDA (2±9%, n=7, $p>0.05$). CaV3-currents were potentiated by train stimulation (39±8%, n=8, $p<0.05$), whereas AMPAR-mediated currents were not altered (6±6%, n=6, $p>0.05$). Increase of CaV3-currents could be mimicked by agonistic activation of NMDARs with brief superfusion of NMDA (30 microM) (97±25%, n=7, $p<0.01$), which was suppressed by PPDA (11±4%, n=7, $p>0.05$), and, surprisingly, prevented in CaV3.2-/- mice (6±5%, n=10, $p>0.05$). Altogether, our data indicate that repetitive activation of GluN2C-NMDARs facilitate recruitment of CaV3.2 channels, thus promoting nRt excitability. This suggests that cortical drive triggers activity-dependent changes in specific molecular cores of thalamic sleep rhythmogenesis.
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In vivo measurement of TCA cycle in mouse dorsal hippocampus using 1H-[13C] NMR spectroscopy at 14.1 Tesla

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Investigating brain metabolism in vivo requires a region-specific approach as it depends on the different cell populations and tissue functionalities. 13C magnetic resonance spectroscopy (MRS), upon administration of 13C labeled probes, is the method of choice to measure metabolic fluxes in vivo. However, due to the lack of sensitivity of 13C, this technique has been limited to large regions of interest, for humans and rats studies, or ex vivo quantifications on tissue extracts. 13C-indirect detection using 1H-[13C] MRS is a promising tool to investigate region-specific metabolism, giving insight into research for transgenic mouse models of brain pathologies. In 2015, Xin et al. have assessed metabolic fluxes in vivo in a 60 µL voxel including mice cerebral cortex and striatum upon administration of [U- 13C] glucose using a one compartment model to fit the 13C turnover curves. In the present study, we have pushed the boundaries to an even smaller region (16.5 µL) by optimizing the design of a 1H-[13C] surface coil and the implementation of NMR indirect methods, to improve the 1H sensitivity detection. We have investigated the dorsal hippocampus, as this structure is important for many brain functions and implicated in many diseases. Results indicated similar data quality with good GluC4, GlnC4, GluC3, GlnC3, and lacC3 detection with only half of the time resolution loss, which is still sufficient for metabolic fluxes modeling. This technique will thus allow to investigate mitochondrial function in vivo in small regions like the mouse dorsal hippocampus.

SHANK3 controls maturation of social reward circuits in the VTA

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Haploinsufficiency of Shank3, which encodes an excitatory synapse scaffolding protein, is the most common monogenic cause of Autism Spectrum Disorders (ASDs). How reduced Shank3 copy number affects neural circuits to generate ASD-related behaviors, including poor social interactions, remains elusive. Since dopamine (DA) neurons of the Ventral Tegmental Area (VTA) encode social interactions, we tested whether VTA-SHANK3 downregulation affects synaptic maturation and social behavior in mice. To mimic haploinsufficieny, we used shRNA against Shank3, which when applied during, but not following, postnatal maturation persistently altered excitatory transmission onto DA neurons, reduced firing in vivo and impaired social preference. A positive allosteric modulator of metabotropic glutamate receptor 1 (mGluR1) administered before the fourth postnatal week rescued synaptic, circuit and behavioral deficits into adulthood. Thus, Shank3 haploinsufficiency in the VTA impairs postnatal maturation of DA neurons and disrupts social motivation, while mGluR1 modulation during the critical period offers a potential ASD treatment strategy.

Post hoc tracking of in vivo GABAergic synaptogenesis during the early postnatal development

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Studies of inhibitory synapse formation and dynamics have been complicated due to the lack of easily visualisable postsynaptic anatomical proxies, comparable to dendritic spines. Here we took advantage of the post-synaptic scaffolding protein gephyrin, which is highly concentrated in GABAergic and glycinergic synapses.
Electroporating rat pups on the embryonic day E17.5 labels cortical layer 2/3 neurons with the plasmid of our choice. Using a plasmid coding for gephyrin-tomato will produce fluorescently tagged gephyrin in the subset of neurons that were electroporated, and thus labels the gephyrin positive densities. By filling these cells post hoc in fixed slices iontophoretically with a fluorescent dye, it is possible to trace the dendrites in 3D and to locate the gephyrin positive clusters onto the dendritic tree, simultaneously visualizing the dendritic spines with high resolution. This enables us to estimate the in vivo location and density of GABAergic synapses together with the spines at different developmental stages.
Our results indicate that in the rat medial prefrontal cortex the density of GABAergic synapses located on the basal dendrites of layer 2/3 pyramidal neurons steeply increases during the first weeks of postnatal development. This increase can be seen both in clusters located directly on the dendritic shaft as well as those on dendritic spines.
As a conclusion, with the technique we created, it is now possible to study GABAergic synapses on single pyramidal neurons, following various in vivo treatments.

A role for the cation-chloride cotransporter KCC2 in inhibitory synaptogenesis

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UNIGE - CMU

Background: Recent data provide a role for KCC2 in dendritic spine formation and, thereby, in excitatory synaptogenesis. Here we investigated whether this cation-chloride cotransporter is involved in inhibitory synapse formation.
Methods: To visualize inhibitory synapses, we used a molecular construct coding for gephyrin, a major component of the postsynaptic protein network in inhibitory synapses. This EGFP-tagged gephyrin construct was co-electroporated with a plasmid coding for KCC2 into progenitors of layer 2/3 pyramidal neurons by means of in utero electroporation at gestational day 17.5 in rats. To reveal detailed neuronal arbor architecture, electroporated neurons were iontophoretically injected using Lucifer Yellow. Confocal microscopy was used to analyze spatial distribution and density of gephyrin clusters along with their relation to dendritic spines.
Results: Electroporation of KCC2 led to an overall decrease in the number of gephyrin clusters on layer 2/3 pyramidal neurons in the medial prefrontal cortex. Spatial analysis of gephyrin cluster distribution revealed that this decrease is primarily due to the lower number of gephyrin clusters on proximal dendritic segments in within a distance of 40 µm from the cell body. Importantly, an increased dendritic spine density accompanied the decreased gephyrin cluster density on these same proximal dendritic segments of layer 2/3 pyramidal neuron
Conclusion: Precocious expression of KCC2 leads to decreased gephyrin cluster densities in pyramidal neurons. These observations, along with data demonstrating an increase in the number of excitatory synapses in these same cells, suggest a role for KCC2 in the establishment of excitation/inhibition balance during neural circuitry development.

Spinal Cord T-Cell Infiltration in the SNI model of peripheral nerve injury: a time course study

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The immune system participates in development of neuropathic pain following nerve injury. In particular, T-lymphocytes infiltration of the spinal cord following peripheral nerve injury was described as contributor to sensory hypersensitivity. Here we observed with a PCR array that T-lymphocytes attracting chemokines were upregulated after SNI in rat spinal cord. SNI surgery was performed on Sprague Dawley adult male rats. This is one of the experimental models of neuropathic pain, inducing hypersensitivity in the sural territory. BrdU injection and staining for proliferation and immunohistochemistry with antibodies to mark respectively microglia (Iba1), astrocytes (GFAP), T-lymphocytes (CD2) and cytotoxic T-lymphocytes (CD8) were performed. A spinal cord injury model was used as a positive control for T-cell infiltration. In the dorsal horn ipsilateral to SNI, Iba1 and BrdU stainings revealed the microglial activation and proliferation respectively, attesting neuroinflammation with various timecourse. Iba1 expression peaked at D4 and D7 respectively at the mRNA and protein level. Proliferation occurred almost only in Iba1 positive cells and peaked at D2. There were few CD2/CD8 positive cells in contradiction to some published data. We used SCI as positive control for lymphocyte infiltration. We observed a pronounced infiltration of CD2/CD8 positive T-cells, validating our negative result after SNI.

BMP signaling involvement in the lateral hypothalamus development

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Hypothalamus is a very complex structure of the brain and plays important roles in the regulation of body homeostasis. Different hypothalamic nuclei containing different neuronal populations interact with each other and other areas of the brain to accomplish this task. The nuclei located in the lateral hypothalamus are strongly involved in sleep and feeding behavior and any dysfunction of these neuronal population results in disorders like sleep disorder narcolepsy that decreases the quality of life. There are very few reports about the development of the lateral hypothalamus and how this small region precisely controls sleep and feeding behavior. Here by using mouse embryonic stem cells in vitro we succeeded to have direct access to this region. Our in vitro produced neurons, specifically MCH neurons, showed expression of Mch, Gad67 and Map2 genes both at mRNA and protein levels. The results showed that BMP signaling but not SHH signaling plays a major role in the generation of these cells exerting their effect from the beginning of neural induction. The Pax2 gene as one of the major transcription factors was shown to be strongly inhibited in this process.

Neurological or Psychiatric Conditions

Predicting pure amnestic mild cognitive impairment conversion to Alzheimer's disease using joint modeling of imaging and clinical data

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Predicting the conversion of amnestic mild cognitive impairment (aMCI) to Alzheimer's disease (AD) is a challenging problem for which machine learning could be of great use. In this work, we aim at assessing the independent and joint value of imaging (structural MRI [sMRI], resting-state fMRI [rsfMRI]) and clinical data in classifying stable versus progressive aMCI. We use baseline imaging and clinical data from 22 MCI, among whom 11 have converted to AD at follow up, and 11 have not. We extract both high and low dimensional features for imaging data, and deploy a random forest classifier to discriminate between MCI converters and nonconverters.

While baseline clinical data does not allow predicting conversion of aMCI to AD, rsfMRI yields accuracies of up to 82% (consistent across 2 atlases). These findings are extremely promising, considering that no previous studies have deployed pattern recognition tools on rsfMRI for conversion prediction. Using sMRI, we reach up to 77%; these results are in line with what is reported in the literature; however, it is important to note that most papers have used large datasets such as ADNI or AddNeuroMed. The use of joint imaging and clinical modalities yields up to 77% accuracy, with imaging data weighting more than clinical data in the classifier's decision. The highest prediction accuracy that we reach is by combining both imaging modalities (86% accuracy, 91%).

Dysregulation of energy balance in Crtc1 mutant mice

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Obesity is a growing health concern worldwide. This pathological condition is due to an imbalance between energy intake and energy expenditure. CRTC1 (CREB-regulated transcription coactivator-1) controls the transcription of many CREB-target genes, some of which are involved in energy balance. Previous published observations show that CRTC1 is strongly expressed in the hypothalamus, a key brain structure in energy regulation, and mice lacking Crtc1 present an obese phenotype.
The aim of this work was to investigate the role of CRTC1 in energy intake and expenditure in Crtc1 knock-out mice. Alterations in energy intake were assessed using three different approaches: measuring body weight and food consumption, evaluating the expression of multiple genes in the arcuate nucleus of hypothalamus by qRT-PCR, and determining the integrity of the reward system by testing the preference and the motivation for saccharine. Finally, the influence of CRTC1 on energy expenditure was assessed through the measure of locomotor activity.
Our results show the presence of a sexual dimorphism in the obese phenotype of Crtc1-/- mice: males gain more weight than females and are hyperphagic. Moreover, only in males, obesity is accompanied by changes in the expression of energy balance-related genes. No difference in saccharine preference has been found, whereas the lack of Crtc1 seems to reduce motivation for saccharine in both sexes. Finally, Crtc1-/- mice show a perturbed pattern of activity and food consumption both in the light and dark phase of the daily cycle.
Collectively, these findings clearly confirm a role of CRTC1 in the regulation of energy balance.

Abnormal neural processing of social feedback in borderline personality disorder

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Borderline personality disorder (BPD) is characterized by affective dysregulation, instability of interpersonal relationships, and marked impulsivity. Marked impulsivity, which maybe unfavorable for balanced social interactions, suggests impaired activity in reward related brain networks. Yet, how BPDs process socially evaluative feedback remains poorly understood. We hypothesized that BPDs and healthy controls (HCs) will differ in how they process social contexts. We thus predicted that BPDs would show increased brain response to cues indexing a social-context while showing abnormal response to social feedback in areas involved in the processing and evaluation of socially rewarding/punishing stimuli. We acquired fMRI data from 20 women with BPD and 24 age matched, female, HCs while they performed a reward-related task in which cues and feedbacks were either social or non-social. BPDs had increased activity for social-cues in the STS (an area critically involved in the perception of intentions of others). We found that BPDs showed decreased bilateral amygdala activity for social feedback. BPD patients showed increased activity in the MD, an area important for saliency and conditioning. Finally, BPDs showed hyper activation for the social aspects of our task in the anterior OFC (an area important for value representation). A gPPI analysis of the MD showed disruptions across the meso/limbic regions during social versus non-social feedbacks.

Altogether, these results suggest an alteration of the neural processing of social contexts and signals in BPD. Taken together, these results shed light onto why patients suffer from difficulties in adapting their behavior, particularity in the context of interpersonal relationships.

Endophenotype of Schizophrenia: Electrophysiological correlates of Visual Backward Masking in Schizotypy

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For the past decade, Herzog and colleagues have defined a potential endophenotype for the schizophrenia continuum called the "Shine-Through paradigm", based on Visual Backward Masking (VBM). A vernier (i.e. the target) is followed by a mask and participants have to discriminate the vernier offset (left versus right). The task is challenging because it requires fine spatial discrimination under strong temporal constraints (Chkonia et al., 2010).
Schizophrenia patients have stronger masking deficits compared to healthy controls. In the electroencephalography (EEG), patients show a weaker neural response at around 200ms after stimulus onset (Plomp et al., 2013).
Masking deficits have also been reported in non-clinical population of the schizophrenia continuum (i.e., schizotypy) as determined by the self-reporting questionnaire "O-LIFE", which assesses three dimensions, Unusual Experiences, Cognitive Disorganization (CogDis), and Introvertive Anhedonia (Mason et al. 2005). CogDis shows the strongest correlation with VBM deficits (Cappe et al., 2012).
Here we investigate the electrophysiological correlates of VBM in schizotypy. Thirty-six healthy students scoring either high or low in the CogDis dimension have been tested. Participants scoring High in CogDis show similar deficits compared to schizophrenia patients but to a lesser extent (i.e., reduced EEG amplitude). The results reinforce the idea of a continuum between schizophrenia and schizotypy susceptible to masking deficits.

Oxidative stress in aging and Alzheimer's disease

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Today, Alzheimer's disease is one of the most important age-related neurodegenerative diseases, but its etiology remains still unknown. Oxidative stress is increased by aging and it was found to be associated with several neurodegenerative diseases including Alzheimer's disease. Here, human autopsy tissues, from frontal cortex of mild and severe Alzheimer's and control's brain, were used to determine the influence of oxidative stress on protein expression. Proteins were studied by 1D and 2D electrophoresis, Coomassie blue staining, Western blots and immunostaining for different proteins of interest and also for post-translational modifications including S-nitrosylation and carbonylation. Carbonylated proteins were detected by derivatization of the carbonyl groups with dinitrophenylhydrazine (DNPH), followed by immunostaining against DNP molecule. In addition, differential infrared dye labeling of thiol groups (DIGE) was used to study cysteine oxidation. Our results showed an increase in protein carbonylation and S-nitrosylation levels in Alzheimer's group compared to control group using 1D analyses. Furthermore, 2D analyses of carbonylated proteins followed by LC MS/MS ID identification showed an increase in the carbonylation levels of several proteins such as synaptic and cytoskeletal proteins and energetic enzymes. Interestingly, Glutamine synthetase was strongly carbonylated at early stage. In parallel, DIGE results showed an alteration of cystein oxidation between proteins from Alzheimer's and control's groups. Among these oxidized proteins, GFAP and tubulin were highly oxidized during AD. These results revealed an important role of oxidative stress during Alzheimer's disease progression since some proteins were oxidized at early stage of the disease.

Genetic editing with the CRISPR/Cas9 system for Huntington's disease

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Huntington's disease (HD) is a neurodegenerative disorder caused by a pathological CAG expansion at the 3' end of the first exon of the huntingtin gene (HTT). Currently, there is no efficient treatment for HD. Editing of the mutant HTT gene with the Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) system represents a new and promising approach. Recognition of the HTT target sequence by a single-guide RNA sequences (sgRNA) and the Cas9 protein is inducing DNA double-strand breaks (DSB), which activate endogenous cellular repair pathways. Non-homologous end joining (NHEJ) will introduce small insertions/deletions (indels) that alter the reading frame of HTT gene while homologous directed repair (HDR) is activated in the presence of a DNA template. Both approaches would lead to a definitive loss of mutant HTT expression.

To validate the approach and optimize the delivery of the CRISPR system with viral vectors, we first targeted artificial sequences containing fluorescent reporter genes in HEK 293T cells. Furthermore, targeting of a genomic integrated reporter gene in neurons and in astrocytes resulted in an efficient gene disruption and was associated with a loss of fluorescence in vitro and in the mouse striatum.

We developed multiple strategies to disrupt the mutant HTT gene. Quantification demonstrated a high rate of indels, leading to a strong reduction of HTT protein in HEK 293T cells, mouse cortical neurons and human iPSC-derived neurons. Blocking HTT expression in cellular HD models improved several physiopathological parameters. We are currently evaluating the impact of allele or non-allele specific mutant HTT editing in human neurons from HD patients. Altogether, these data demonstrate the potential of the CRISPR technology as therapeutic strategy for HD.

Neurons and astrocytes contributions to striatal degeneration and behavioral deficits in Huntington's disease

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Huntington's disease (HD) is a neurodegenerative disease caused by an autosomal dominant mutation on the huntingtin gene (HTT). Recent data have suggested the implication of non-neuronal cells in the disease, in particular astrocytes. These observations underline the need to better characterize neuron-astrocyte interactions specifically in HD. A strategy consists to model the disease using cell-type specific viral vectors. In particular, Adeno-Associated Viruses (AAV) offer the possibility to shift their tropism from neurons to astrocytes using specific capsids and promoters. In this study, we used an AAV2/5 to express a short mutant HTT fragment under the control of a neuronal or an astrocytic promoter in the mouse striatum. We first show that the combination of AAV2/5 and the chicken-ß-actin (CBA) promoter or Gfa2(b)3 promoter leads to a high expression of a reporter gene specifically in neurons or in astrocytes. We replaced this reporter gene by a cassette expressing the first 171aa of the HTT with 82 or 18 CAG to study the contribution of each cell population to HD. Expression of mutant HTT selectively in neurons leads to progressive motor alterations and increased anxiety, whereas expression in astrocytes leads to a less severe phenotype. We furthermore characterized several cellular and molecular hallmarks, two profiles of huntingtin aggregation were observed between the neuronal and the astrocytic model, leading to specific cellular dysfunctions. We finally used co-injections to express mutant HTT both in neurons and in astrocytes to evaluate the potential synergistic effect of the mutant protein in both cell types.

EEG resting-state directed connectivity alterations in temporal lobe epilepsy vs healthy controls

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The characterisation of pathological networks in the absence of interictal epileptiform discharges (IED) could have an important diagnostic/prognostic value. Using high-density EEG, we investigated resting-state directed brain connectivity independent from interictal epileptiform discharges (IED) in left and right temporal lobe epilepsy (LTLE and RTLE) compared to healthy controls.

Twenty LTLE, 20 RTLE patients and 20 healthy controls underwent a resting-state high-density EEG. Source activity free of IED was obtained for 82 regions of interest (ROI). Granger-causal modeling was applied to the source signal of all ROIs to estimate the summed outflow (SO) from each ROI (to all others) and pair-wise connectivity between ROIs. Correlations with the duration of the disease were computed.

In all regions and groups, SO peaked in the alpha band. The highest SO occurred in the hippocampus, amygdala, parahippocampus, posterior cingulate cortex (PCC) and anterior cingulate cortex (ACC), which are known to belong to the Default Mode Network. The SO from these regions was significantly reduced in patients compared to controls. The strongest connections in controls were from PCC, while in both patient groups these were from ipsilateral hippocampus. In RTLE, disease duration negatively correlated with the outflow from the contralateral hippocampus. In both patient groups, age negatively correlated with the outflow from the piriform cortex. Outflow from the ACC was lower in patients with learning deficits or depression compared to patients without impairments and to controls.

The resting-state network reorganization in the absence of IED in TLE could constitute an important EEG-based biomarker of TLE.

Increased intra-participant variability in schizophrenia: evidence from single-trial EEG analysis

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Visual deficits in schizophrenic patients are of particular interest because they reflect the deficient circuits of information processing in the brain. In our previous work, we showed that schizophrenic patients have decreased peak amplitudes and reduced cortical activity when performing a vernier offset discrimination task. However, it remains unclear whether these reduced amplitudes are caused by diminished activity or larger variability of amplitude peak latencies. Here, we analyzed the patients' deficits in terms of intra-participant trial-by-trial variability. ERPs variability were estimated using a two-step graph-based method. We found that patients had larger N1 peak amplitude latency variability than matched controls. After correcting for the latency variability, the patients still showed smaller and more variable N1 peak amplitudes than controls. Hence, peak amplitudes are both diminished and highly variable in the patients. These observations provide empirical evidence in support of theories of increased noise in patients with schizophrenia.

Functional network alterations in 22q11.2 deletion syndrome and associations with prodromal psychosis

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UNIGE

The 22q11 deletion syndrome (22q11DS) is a genetic disorder characterized by a high risk to develop schizophrenia. Neuroimaging studies performed in this population aim at better understanding the neural correlates of psychosis development. Evidence shows the presence of brain connectivity alterations in schizophrenia and in 22q11DS, where strong structural alterations of the brain connectome have been described. However, functional connectivity remains poorly investigated in this population. We will present two studies that aim at describing the alterations of the functional network in 22q11DS. For both studies, a brain graph composed of 88x88 regions of interest (AAL atlas) is obtained, for each participant, and the connectivity between each pair of brain regions is obtained by computing the Pearson correlation coefficient between denoised and filtered averaged time-series. Our first analysis used pattern recognition as a statistical test to compare the functional connectomes of the patients versus healthy controls and revealed a predominant frontal dysconnectivity associated to the microdeletion. A high accuracy was also obtain for the identification of the patients with prodromal psychotic symptoms from the rest of the patients, proving the presence of specific functional connectivity alterations associated to psychosis. Our second analysis used a modularity algorithm to study the community structure of the functional brain network in 22q11DS and showed the presence of a disorganization of the network that particularly affects frontal and visuo-spatial structures. Furthermore, by repeating this same analysis in two age subgroups our results suggest the presence of a delayed functional network maturation in 22q11DS.

Non-transient and patient-specific functional connected epileptic networks

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Background. Focal epilepsies are associated to dysfunction of a network rather than to a single focus. EEG-fMRI related to interictal epileptiform discharges (IEDs) maps such network but the preservation of its structure between the occurrence of IEDs and its role in brain functional organization remain poorly understood. Aims of this study were to assess if the epileptic networks exhibit coherent fluctuations independent from the scalp-detected IEDs and to investigate patient-network specificity.
Methods. We acquired EEG-fMRI resting state in 8 drug-resistant focal epilepsy patients, having multifocal IED-correlated BOLD response and maximal t-value in the IEDs field. For each patient, we performed seed-based Functional Connectivity (FC) and we compared the FC-maps before and after regressing out the IEDs in terms of statistical power (max and mean t-values) and percentage of spatial overlap. In each patient we tested for epileptic network specificity, using resting state fMRI of 20 healthy subjects FC maps based on the patient-seed and we evaluated the difference between each patient and the group of healthy subjects (Wilcoxon rank-sum test). Finally, we built the commonality map of each healthy group and we looked for the patient specific patterns.
Results. At group level, the one paired t-test on the mean and max t- values revealed that the FC map was altered ($p<0.01$) after regressing out the IEDs, even if the averaged spatial overlap resulted in 85±12 %. Each patient showed a FC map statistically different ($p<0.001$) from healthies with increased ipsilateral, but decreased contralateral connectivity to the IEDs focus.

Heroin-evoked synaptic plasticity in the Nac driving cue-evoked relapse

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The psychic dependence characterizing addiction is thought to be independent of the class of drug. Indeed a wide range of addictive drugs can lead to behavioral changes and addiction. One of the mechanisms proposed to explain the development of an addiction is a modification of the physiological synaptic plasticity. Two of the main classes of the addictive drugs are the opioids and the psychostimulants. Despite different molecular targets and mechanisms of action, both drugs increase the dopamine (DA) level in the mesolimbic system, especially in the Nucleus Accumbens (NAc). Whereas cocaine-evoked synaptic plasticity in the NAc has now been deeply investigated and causally linked to addiction-related behaviours, it is still not known if similar cellular adaptations are induced across different class of drugs.
Using a self-administration (SA) mouse model of cue-associated heroin seeking combined with ex vivo electrophysiology in optogenetically indentified circuits, we propose in the present study to investigate the input specific plasticity of excitatory transmission linked to particular component of addiction-related behaviours.

Propagating spikes are associated with the emergence of neocortical high-frequency oscillations remote from the epileptic focus in the mouse-model of temporal lobe epilepsy

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In focal epilepsies, the epileptic focus may affect the activity of remote brain regions leading to the progressive development of an epileptic network. Fast ripples (FRs, 200-550 Hz) are believed to be a marker of epileptogenic brain areas and have been used to locate epileptic foci. We hypothesize that FRs could be used to locate normal brain regions progressively recruited within the epileptic network, using the kainate mouse-model of hippocampal sclerosis.

23 adult mice were recorded with 32 surface electrodes prior to injection of kainate in the left hippocampus (LH), then at day 7, 14 and 28 after injection. Surface recordings allowed us to map the epileptic network and to identify brain regions expressing FRs. The epileptic network was characterized by propagating spikes (PrS) starting from the hippocampus and propagating to all contacts in < 20 msec. Their occurrence increased throughout the disease. After kainate injection, FRs increased massively over the LH and also progressively over the right hippocampus and neocortical frontal areas. Importantly, neocortical FRs were tightly coupled with PrS: (i) their frequency of occurrence increased in parallel, (ii) they were preferentially expressed during PrS and (iii) they specifically appeared in target regions of the PrS. Intracortical recordings using 4x16 channels confirmed the network involving at least both hippocampi and the left primary motor cortex. Onset of motor cortex-FR was phase-coupled with the LH-LFP.

Finally, we show that PrS with the highest amplitude were those associated with frontal FRs, suggesting that neocortical-FRs are elicited by the strongest epileptic spikes.

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.

We compared PVI, PNN and microglia level in GCLM-/- and WT mice at peripuberty and in adulthood, with an additional oxidative insult from postnatal days P10-20. This treatment led to a decreased PVI+ and PV-PNN+-IR, increased oxidative stress level and microglia activation in adult GCLM-/-, although this effect was more pronounced at peripuberty, 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 and MMP9-IR in GCLM-/- at P40. A specific MMP9 inhibitor prevented RAGE shedding and microglia activation, suggesting that this treatment may 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.

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.

Relevance processing in the amygdala, an intracranial electroencephalography (iEEG) study

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UNIGE & HUG

The Component Process Model (Scherer 2001) suggests that the perception of an emotion is a dynamic process, where different components of evaluation take places consecutively and interact with each other. In this model, the initial component of a stimulus has been proposed to be the relevance, meaning its intrinsic value given the circumstances. This initial component is supposed to modulate the attentional resources allocated to its processing and the degree of motivation to take subsequent actions (Scherer 2009). The amygdala, given its well-known implications in the evaluation of potential danger, has been hypothesized to work as a system for relevance detection (Sander, Grafman & Zalla, 2003).

In this iEEG study, we investigated the role of the amygdala to process the relevance of emotional and non-emotional visual stimuli. We present here preliminary results of two experiments obtained in two implanted patients with intractable epilepsy.

For both experiments, the relevance was manipulated solely by the task instructions. In one experiment, during the first block, patients had to detect fearful faces (relevant) among neutral ones (irrelevant), and, during the second block, they had to detect neutral faces (relevant) among fearful faces (irrelevant). Local field potential (LFP) analyses indicate that early amygdala responses differ between relevant and non-relevant emotional stimuli. In another experiment, patients performed the same task but this time with geometrical shapes instead of faces. Similarly, LFP analyses suggest that the amygdala responds differently for relevant and for irrelevant stimuli. Together, those results suggest that the amygdala is involved in relevance detection.

Neuron-glia interactions

3D volume imaging of calcium dynamics in astrocytes

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UNIL-DNF

Astrocytes display a complex spatiotemporal pattern of intracellular Ca2+ dynamics ranging from local signals, confined to microdomains, to broader Ca2+ elevations, involving larger portions of processes and possibly extending to cell body or neighboring cells. Even though most of the studies performed on astrocytic Ca2+ signaling to-date used confocal or two-photon laser scanning microscopy in a single focal plane (often about 1 µm thick and arbitrarily selected), astrocytes are known to be highly ramified and tridimensional cells, with several processes interacting with environing cells and structures, notably neuronal synapses and blood vessels in multiple focal planes.
In this study, we used an Acousto-Opto Deflector (AOD) system and a rapid piezo device, allowing fast 3D scanning, in combination with two-photon microscopy, to image the entire 3D volume of astrocytes in hippocampal slices of p30-40 mice. To detect calcium elevations, we used transgenic mice that conditionally express a Genetically Encoded Calcium Indicator (GCaMP3) specifically in astrocytes. Finally, we developed a dedicated framework for processing and analysis of the “big data” generated by our 3D+t multispectral acquisitions.
Preliminary analysis of our 3D recordings indicates that basal Ca2+ activity in different volumetric regions of an astrocyte (soma, processes, end-feet) is definitely asynchronous and can’t be predicted from the activity detected at any moment in any other region of the cell.
We expect that our approach will reveal new features of astrocytic Ca2+ signaling that will help us to better understand the role of these cells in physiological and pathological brain process.
This research is supported by ERC Advanced grant 340368 "Astromnesis" and SNSF grant 31003A-140999 to AV.

Astrocyte swelling in response to neural activation: Role of cotransporters

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CNP/CHUV

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, for osmotic reasons, by transmembrane water movements, which challenge the astrocyte volume constancy. Consequently, taking into account cell volume homeostasis is an essential condition for survival, in particular in the brain where consequences of volume deregulation can be dramatic (oedema, ischemic and hemorrhagic strokes, etc.). 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, which combines both quantitative phase digital holographic microscopy (QP-DHM) and epifluorescent imaging. This approach thus provides the original ability to simultaneously monitor both cell volume and transmembrane water movements as well as the intracellular concentrations of the specific ionic species including [Na+]i and [K+]i .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.

However, these multimodal measurements have permitted to stress that water influx are temporally offset by the GLAST-mediated [Na+]i 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. In addition, astrocyte cell volume regulation after glutamate application strongly depends on extracellular [K+].

Sensory and Motor Systems

Are motor-related electro-cortical markers modulated by an acute endurance exercise?

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Voluntary movements are preceded by a low frequency brain activity that occurs about 1.5 seconds before movement onset. This movement-related cortical potential (MRCP) is influenced by various factors such as level of intention, pacing of movement, precision, force exerted, and fatigue. The purpose of this study is to investigate the effects of two endurance exercises with moderate and high intensities on the preparatory phase of voluntary movements using surface EEG.

Sixteen trained athletes performed two successive exercises on a cycle ergometer. Before, between, and after the two sessions of exercise, surface EEG was recorded during 60 self-paced leg extensions. The central MRCPs were segmented and averaged into non-overlapping epochs from 2500 ms before and 500 ms after the leg movement onset. The readiness potential (RP) and the motor potential (MP) were used for analyses. Neuromuscular data were also collected using the percutaneous neuromuscular stimulation technique.

The analyses revealed a reduction in the maximal force associated with a reduction in the voluntary activation level and the doublet force twitches. The MRCP mean negativity amplitudes during RP and MP also decreases after both exercises.

The results show that a whole-body exercise induces a reduction in the MRCP amplitude associated with a significant reduction in force production. While an increase in the negativity has been show to compensate peripheral fatigue in single-joint exercise, a decrease seems to be indicative of a reduction in the amount of energy required to plan the task.

Adult neural progenitor cells auto transplantation in a non-human primate model of Parkinson's disease: a pre-clinical study

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UniFR

Autologous cells transplantation overcomes several issues raised by the use of human ESC including ethical controversies and immune limitations. The present investigation intended to assess the impact of autologous neural cells ecosystem (ANCE) transplantation in four cynomolgus macaque monkeys exhibiting parkinsonian symptoms.

To achieve this goal, monkeys were extensively trained to perform fine manual dexterity tasks as well as a reach and grasp drawer task (Schmidlin et al., 2011) before undergoing systemic MPTP lesions. During the MPTP phase, small cortical biopsies were performed and the gray matter material obtained put into culture according to the protocol developed by Brunet and colleagues (Bloch et al., 2014; Brunet et al., 2002). Additionally, at all phases of the protocol, the integrity of the nigro-striatal system was followed-up by 18F-dopa PET scan. Finally histological analysis allowed determining the fate of the implanted cells and their potential mode of actions.

Out of the four animals, two were severely affected by the MPTP lesions whereas the other two exhibited mild symptoms. Furthermore, the 18F-dopa striatal uptake was reduced by about 80% in three of them. Six months following ANCE transplantations, all monkeys presented significant improvement of their motor impairments (spontaneous activity, manual dexterity, posture, etc.). This functional recovery was accompanied by an increase of 18F-dopa striatal uptake.

Taken together these new data open new therapeutic perspectives for the ANCE approach regarding neurodegenerative disorders like Parkinson's diseases.

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 neural retina and the choroid. Its main contributions to the visual process are the synthesis and recycling of the chromophore required for phototransduction, the phagocytosis of shed photoreceptor outer segments, the regulation of fluid and nutrient flow between the retina and the choroid. 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 is particularly worth to answer these important challenges.
Here we present a reliable, xeno- and serum-free method to generate hRPE from iPSCs in culture. Starting from feeder-free culture conditions we established a three-step protocol able to induce the typical RPE cobblestone appearance, and pigmented foci as early as 23 days after differentiation. The cells are characterized by their pigmentation, the expression of mRNAs of typical RPE markers associated with the retinoid cycle (CRALBP, RPE65), chloride channels (BEST1), phagocytosis (MERTK) and specific coexpression of transcription factors (PAX6, MITF). The presence of protein involved in the tight junction formation (ZO-1) was revealed by immunocytochemistry.
In conclusion, the presented protocol provides a consistent method to generate hRPE from pluripotent stem cells which will be utilised to generate RPE-like tissues from hiPSCs of affected patients with the aim to perform in-depth study of diseases mechanisms and test new treatments.

Subject-specific involvement of the primary motor cortex during implicit motor imagery

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Mental imagery – whether we consider its motor or sensory modalities – is known to rely on a partially overlapping neural network with respect to its corresponding non-imagery, overt behavior. Implicit motor imagery is commonly defined as the unconscious, non-sensorial, internally-generated reproduction of motor actions, and it is most commonly investigated via motor rotations through the "hand laterality judgment task". Both behavioral and neuroimaging data have shown that the sensorimotor network, including motor representations, plays a critical role in implicit motor imagery, but the scientific community is still disagreeing on its exact neural underpinnings. The strongest conflict lays in the participation of the primary motor cortex (M1) into this imagery process, since very diverging results have been obtained within and across different techniques. In particular, several Transcranial Magnetic Stimulation (TMS) studies have repeatedly confirmed or refuted M1 involvement. Even among the studies reporting M1 activity, its temporal dynamics is still disputed.

We claim that this disagreement across studies could be driven by the high variability of the subject-specific performance of motor rotation. Indeed, average response times can double from one subject to the next, and therefore the commonly used stimulus-locked paradigms can lead to the TMS pulse being administered at very different stages of the task processing across subjects. Here, we will present pilot data of single-pulse TMS during hand laterality judgment task, in which the pulse timing is calculated as a percentage of the subject- and condition-specific average response time, instead of a fixed delay after stimulus onset.

Optogenetic loss-of-function mapping of cortical motor circuits involved in voluntary action

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UNIGE - CMU

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. 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 automated behavioral control systems.
To transiently silence specific motor areas, we used a high resolution optogenetic mapping method. The different motor areas in the contralateral hemisphere were inactivated through the intact skull using a laser scanning system.
We found that inactivating forelimb related areas impaired the performance at several levels. The ability to plan the appropriate movement, as well as the execution of forelimb movements were strongly affected when inactivated early or late during the trial, respectively.
These results confirm the important role that motor cortex circuits play different aspects of in choice making, planning and execution of goal directed forelimb movements in mice.

Characterization of dendritic structure and dynamics of superficial VIP cells in the mouse somatosensory cortex

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UNIGE - CMU

A fraction of the cortical vasoactive intestinal polypeptide (VIP)-expressing interneurons are thought to specialize in disinhibitory control of pyramidal cells. Some VIP neurons located in superficial cortical lamina bear spines. Here we sought to provide insights into the spine dynamics on these cells in order to further our understanding of how long-range excitatory inputs may modulate local disinhibition. We used VIP-Cre transgenic mice in combination with Cre-dependent AAV vectors encoding GFP to image spiny superficial VIP neurons in the mouse somatosensory cortex in vivo. Anatomical reconstructions suggest that the morphology of these spiny neurons display similarities to a previously described class of multi-polar VIP neurons in layer 2. Longitudinal imaging data suggest that the spine dynamics are different from those on pyramidal cells. A relatively large fraction of spines has intermediate life times (varying from several days to weeks), but the total population of spines is less stable than on pyramidal cells. These data suggest that the levels of disinhibition are adjustable though the dynamic regulation of the strength and source of excitatory inputs on VIP cells. In order to identify excitatory inputs that are being regulated by these spine dynamics we set out trans-synaptic labeling experiments, using EnvA-pseudotyped rabies virus from which the gene encoding the coat glycoprotein (G) is removed. This virus can only infect neurons that express the receptor for EnvA (TVA) and reproduce if in these cells G is expressed. We expressed TVA and G in VIP-Cre neurons, using Cre-dependent AAV vectors, superinfected them with rabies, and analyzed transsynaptic labeling of presynaptic neurons. Preliminary results indicate that in addition to many local pyramidal cells, long-range inputs from the thalamus and other cortical regions impinge on VIP neurons in S1. Together, this suggests that spines on VIP neurons may regulate the extent of excitatory input from various local as well as distant regions in the brain.

Signalling and Excitability

Characterizing connectivity and signal propagation in the lateral amygdala through local networks

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Fear conditioning combines an unconditioned stimulus with a conditioned stimulus (CS) so that the CS alone can subsequently elicit fear-related responses. While plasticity of converging signals onto a single lateral amygdala (LA) neuron has been extensively studied, little is known about the role of connections between LA neurons in fear-memory encoding.

We hypothesize that fear signals are re-integrated in the LA through local neuronal assemblies. We used whole-cell patch-clamp recordings to simultaneously access up to 12 neurons, with the aim of mapping network topology and studying the LA-to-LA synapse. We recorded from 571 neurons whose connectivity was assessed by delivering, successively, a train of 8 pulses at 20 Hz and monitoring for induced post-synaptic potentials.

We observed 2% connectivity, with the chance to observe a connection decreasing with inter-somatic distance. This suggests a "small-world" network organization. Plasticity was assessed in 13 connected neurons by pairing 15 pre and post-synaptic trains, with a 10ms delay between pre- and post- synaptic stimulation. This led to a redistribution of the amplitude of EPSPs with a high-amplitude first response for 4 connections. We were also interested in the spatiotemporal progression of a signal within the LA network. To this end, we monitored the preferred path of a spontaneous epileptogenic signal which spread from caudal to medial to rostral LA with a delay of 68±31ms between caudal and rostral ends. Interestingly, this path coincides with a caudal termination of external capsule fibers in the LA (input) and rostral projections from the LA to the basolateral amygdala (output).

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 regulate fear expression and extinction. Additionally, it has been hypothesized that oxytocin (OT) and its receptor (OTR) modulate those pathways. In mPFC, OTR have been found in somatostatin+ cells, known to inhibit principal neurons (PN), but also the parvalbumin+ neurons (PV+), thus, the OTR signaling could be involved in an inhibitory circuit within the mPFC cells that excite the amygdala.
Consequently, we traced the projections from the mPFC to various areas in the amygdala by retrograde labelling. At the moment, successful injections of retrograde fluorescent beads have been performed in the amygdala, leading to fluorescently labelled cell bodies in the L5 of mPFC; we coupled this tracing technique with patch clamp recordings, in order to identify the sensitivity of amygdala projecting neurons in the mPFC, to OT.
We found that OTR activation increases post synaptic currents (PSCs) in 34.7% of mPFC cells, disregarding of its cell type (IN's & PN's). Secondly, OTR activation in BLA projecting cells within the layer 5 of the prelimbic cortex (PL) increases PSCs and this involves GABA-A R, implying that the OTR signaling could modulate the excitatory projections from PL to BLA, the triggering pathway for fear expression.
Finally, OTR activation increases inhibitory post synaptic currents (IPSC's) in PN (L5) of PL. Overall, the data suggest that OTR activation in PL inhibit the excitatory projections to BLA, and thus the fear expression pathway.

Techniques in Neuroscience

Quantifying indices of short- and long-range white matter connectivity at each cortical vertex

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UNIGE

Several neurodevelopmental diseases are characterized by impairments in cortical morphology along with altered white matter connectivity. However, the relationship between these two measures is not yet clear. In this study, we propose a novel methodology to compute and display metrics of white matter connectivity at each cortical point. After co-registering the extremities of the tractography streamlines with the cortical surface, we computed two measures of connectivity at each cortical vertex: the mean tracts' length, and the proportion of short- and long-range connections. The proposed measures were tested in a clinical sample of 62 patients with 22q11.2 deletion syndrome (22q11DS) and 57 typically developing individuals. Using these novel measures, we achieved a fine-grained visualization of the white matter connectivity patterns at each vertex of the cortical surface. We observed an intriguing pattern of both increased and decreased short- and long-range connectivity in 22q11DS, that provides novel information about the nature and topology of white matter alterations in the syndrome. We argue that the method presented in this study opens avenues for additional analyses of the relationship between cortical proper- ties and patterns of underlying structural connectivity, which will help clarifying the intrinsic mechanisms leading to altered brain structure in neurodevelopmental disorders.

5-HT2A receptor SPECT imaging with [123I]R91150 under P-gp inhibition: promising enough?

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P-glycoprotein-induced (Pgp) radiotracer efflux in the blood-brain barrier may hamper neuroreceptor quantification in nuclear imaging. Thus, pharmacological P-gp inhibition with tariquidar (TQD) is considered a promising strategy for the augmentation of radiotracer brain uptake. However, no study has validated the robustness of quantitative studies under these conditions. For this reason, we studied the effect of a TQD pretreatment on 5-HT2A imaging with [123I]R91150 and compared results with those obtained in a model of complete absence of P-gp activity, the Mdr1a knock-out (KO) rat.

Ex vivo autoradiography was performed in TQD (15 mg/kg) pretreated wild-type (WT-TQD), in Mdr1a KO and untreated WT rats for Standardized Binding Ratio (SBR) estimation. In vivo dynamic SPECT imaging and quantification of the 5-HT2A receptor was performed using 1) full kinetic modeling with arterial blood radiotracer measurement and 2) a simplified Specific Uptake Ratio (SUR), using image-derived radiotracer binding in cerebellum as a reference region. Results were statistically analyzed using repeated measures ANOVA.

SBR values differed between WT-TQD, Mdr1a KO and WT rats in a region-dependent manner ($p<0.0001$). Similarly, SUR demonstrated values that were 2.99±0.53 times higher in the WT-TQD group than in MDR1a KO rats, with the difference between groups being region-dependent ($p<0.001$).

In conclusion, P-gp inhibition with TQD, although substantially augmenting radiotracer uptake in the rat brain, leads to region-dependent effect, with a notably sub-optimal effect in cerebellum. This warrants attention when quantitative studies are performed and underlines the usefulness of the Mdr1a KO rat in translational studies involving 5-HT2A receptor SPECT imaging.

Evaluation of Source Functional Connectivity in Low-Density EEG

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In order to study the slow alternations of brain activity, long-term EEG monitoring is a promising way. Nonetheless, the systems designed for long-term and portable monitoring of patients usually work with limited number of electrodes, which leads to low-density EEG (ldEEG). With regards to ldEEG, some useful methods of EEG analysis have limited applications. Functional connectivity (FC) analysis is one of these methods with which changes in a number of psychiatric and neurodegenerative diseases have been detected. However, FC estimation in sensor space is biased due to volume conductance, while because of low surface sampling the source reconstruction of ldEEG is imprecise. This makes developing and testing new techniques for ldEEG a topical objective. In recent years, a method approximating partial spectral covariance (PSC) of the source space through a generalized inverse of the PSC in sensor space has been proposed by Pascual-Marqui et al. It is claimed to be efficient for ldEEG applications. To empirically test this method, we performed EEG simulations considering different configurations of functionally connected cortical sources. In this simulation, we succeeded to approximate the FC for two sources in both high and low density simulated EEG, while the accuracy of FC estimations highly depends on location and distance between EEG sources. These results indicate the limited ability of the method to detect simple patterns of connectivity, while the validity of its application to real EEG data remains questionable.

Other topics

Quantitative analysis of the structural organization of the monkey entorhinal cortex.

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The entorhinal cortex is the main gateway for bi-directional communication between the neocortex and the hippocampal formation. Its superficial layers II and III represent the main entryways for the sensory information processed by the hippocampus, whereas its deep layers V and VI provide the main exit ways through which processed information is sent back to the neocortex. In monkeys, the entorhinal cortex has seven subvidisions. We found that the numbers of neurons in the superficial and deep layers differ between these subdivisions. In the rostral field, 10% of neurons are located in layer II, 56% in layer III, 9% in layer V and 26 % in layer VI. In the intermediate field, 14% of neurons are located in layer II, 41% in layer III, 15% in layer V and 30 % in layer VI. In the caudal field, 15% of neurons are located in layer II, 38% in layer III, 15% in layer V and 32 % 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. We discuss how differences in the relative input/output ratio might contribute to different functions of distinct subdivisions of the entorhinal cortex.

The implication of miRNAs in the regulation of basal MCT2, GluR2/3 and PSD95 expression in cultured cortical neurons

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UNIL

MCT2 is the predominant neuronal monocarboxylate transporter allowing lactate use as an alternative energy substrate by this cell type. It is suggested that MCT2 is upregulated, at the translational level, to meet enhanced energy demands after modifications in synaptic transmission. Indeed, it has been shown that some neuroactive signals implicated in the synaptic plasticity process, such as BDNF, insulin or IGF-1 could significantly increase MCT2 protein expression in primary cultured cortical neurons through a translational regulation at the synaptic level. MicroRNAs (miRs) have been shown to be important regulatory elements in the control of translation of numerous proteins. MicroRNAs are a class of small non-coding RNA molecules negatively regulating gene expression in many tissues including the central nervous system and have been recognized as key regulators of different biological processes, including glucose metabolism. In this study, we hypothesized that some microRNAs could be regulators of MCT2 expression in cortical neurons. To determine if miRNAs could regulate the transcription of MCT2, we used a cell line (ESC) allowing for an inducible knock-down of *Dicer*. With this cell line, which expresses already some MCT2, we have shown that miRNAs repression lead to a decrease of MCT2 protein level. To determine which miRs could be implicated in the regulation of MCT2 expression in neurons, a bioinformatic analysis was performed. This approach predicted numerous candidate miRNAs, including miR-125b, -132, -134 and -212. Then, we confirmed the presence of those miRs in primary cultures of mouse cortical neurons with qPCR and, at the same time, we assessed the protein level of MCT2, GluR2/3 and PSD95 by Western Blot from 7 DIV to 21 DIV. Finally, to determine if miR-125b, 132, -134 and -212 were regulating MCT2 expression, we transfected cultured cortical neurons with the corresponding anti-miRs. Our results revealed an increase of MCT2 protein expression only after anti-miR-134 treatment but not after the other anti-miR treatments and an increase of GluR2/3 and PSD95 protein expression only after anti-miR-212 treatment but not after the other anti-miR treatments. These data suggest that miR-134 and miR-212 could regulate protein level expression of some neuronal metabolic actors such as MCT2 and some synaptic actors such as GluR2/3 and PSD95.

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