Abstract book

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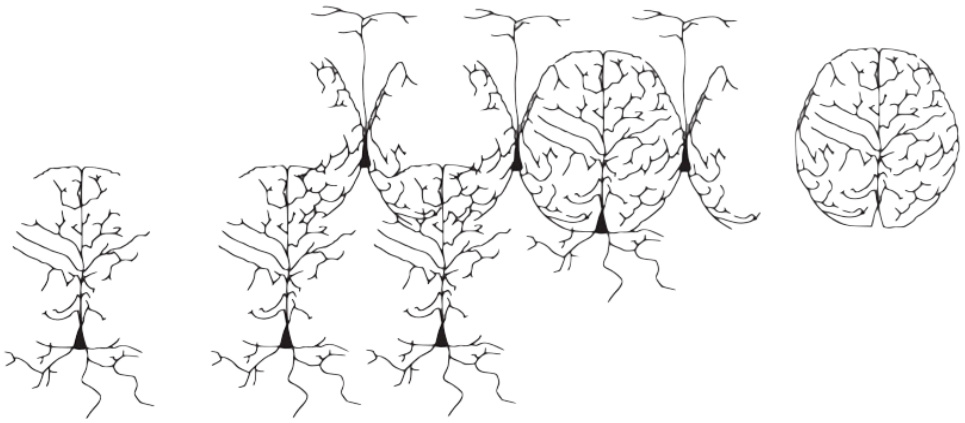

Fonds Jean Falk-Vairant

Association Amicitia

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Autonomic, Limbic, Neuroendocrine or Other Systems

1. Cortical circuits matching body metabolic signals and behavior

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Signals from peripheral organs are known to influence mental processes. Neuroimaging studies have confirmed that cortical areas respond to changes in body physiological conditions and that these fluctuations affect psychology and behavior. Despite their important clinical implications, the pathways underlying these effects have been little explored. We investigated the role of insular cortex (IC) as an interface between interoceptive sensing and cognitive and emotional responses. In vivo glucoprivation by an i.p. administration of 2-deoxyglucose (2DG) decreased anxiety-like traits and compulsion behaviors in mice. This metabolic challenge also induced c-fos expression in a subpopulation of cells in IC, suggesting a putative link between IC metabolic-responsive neurons and behavior. To investigate the underlying cellular mechanisms we performed experiments on acute cortical slices. Whole-cell electrophysiological recordings further evidenced a set of neurons located in deep IC layers that respond to glucose in a cell-autonomous fashion, with either a glucose-inhibited or a glucose-excited phenotype. We are now looking at the identity of these neurons and characterizing the biophysical and molecular components of their responses to glucose changes.

Behaviour, Cognition, Neuroimaging

2. Rhythmic training and executive functioning in seniors with fall risks

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Decline in executive function are common in seniors and contribute to fall risk. Previous work showed that music-based rhythmic training improves balance and reduces falls. Here we aim at assessing the impact of music-based training on both falls and cognitive functions.
During 1 year, 140 participants participate in a weekly exercise training. All participants take part in a clinical study and 34 of them, recruited for an fMRI study, are scanned before and after the training. To assess executive functions, fMRI sessions involve a motor coordination task and a selective attention task with or without music.
Preliminary baseline results indicate that participants have more difficulties to perform multitasking and show greater brain activity in dual-task conditions (coordination task). They also show slower responses to incongruent conditions with increased activation of areas associated with conflict processing as well as different networks according to the emotion evoked by the excerpts.

3. How do negative and positive moods shape face perception?

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It has long been known that high anxious individuals attribute a more negative meaning to ambiguous information. But can such biases be induced transiently in a short-term manner? On the other hand, can positive mood induce the reverse bias? To test this hypothesis, we studied how affect induction and anxiety can affect ambiguous morphed faces interpretation.

We used fearful, neutral and happy video clips to induce negative, neutral or positive affective states. After mood induction, participants classified the expression of faces morphed at varying proportions between fearful and happy expressions.

Following fearful movies, subjects classified ambiguous faces as expressing fear more often than after neutral or happy movies. After joyful videos, especially the more absorbing ones, we also observed a trend toward classifying ambiguous faces as expressing happiness more often than after neutral or fearful movies. Participants who scored high on depression and anxiety scales classified more often ambiguous faces as fearful, independently of mood, confirming the spontaneous tendency to classify ambiguous information in a more negative manner. Interestingly, highly absorbing happy and neutral movie clips reduced the negative bias toward fearful faces.

These results add to the existing cognitive bias literature showing that priming positive and negative cognitions can change the extent to which individuals direct attentional focus or interpret ambiguous semantic information. To our knowledge, these are the first results to demonstrate that short-term affect induction changes the emotional meaning we attribute to facial expressions. This knowledge might be useful in the context of cognitive bias modification in clinical training interventions which aim at modifying biases which confer vulnerability to anxiety.

4. Working Memory Training and Risky Decision-Making: An ERP Study in ADHD and Control Participants

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Patients with a diagnosis of attention deficit/hyperactive disorder (ADHD) are characterized by Working Memory (WM) impairment and by an abnormal sensitivity to reinforcement that is likely to influence cognitive processes such as decision making through unconscious ‘‘somatic marker signals’’ that arise from bioregulatory processes. During decision making it is important to determine whether the subjects are sensitive to the frequency but blind to the magnitude of a penalty/reward. In order to investigate whether a WM training can provoke a neural response having an influence on risky decision making, we designed a study where participants had to perform a probabilistic Investment Game (PIG), modified from the original Gneezy and Potters’ neuroeconomic game (1997).

5. Conspecific objects exhibit preferential multisensory integration

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Rudimentary and complex stimuli, including environmental objects, both elicit multisensory interactions during early post-stimulus stages. Our study assessed whether multisensory processes and their neural mechanisms vary across object categories. Processing of (unisensory) object categories has been typically dissociated between living and man-made categories. Additional evidence points to preferential processing of conspecific stimuli, such as faces or voices. Whether such preferences engender facilitated multisensory integration of some objects over others remains unknown. We recorded 160-channel EEG from 14 healthy adults performing a living/man-made go-nogo categorization involving environmental objects presented as sounds, drawings or auditory-visual pairs. Behavioural analyses were based on the inverse efficiency scores (median reaction time divided by percent correct responses). The 2x3 ANOVA with factors of category (living/man-made) and sensory condition (auditory, visual, multisensory) revealed an overall advantage for discriminating living vs. man-made objects, irrespective of the sensory condition. There was no evidence for multisensory facilitation. The 3x3 ANOVA with sub-categories of living objects (conspecifics, mammals, birds) and sensory condition revealed multisensory facilitation exclusively for conspecifics. EEG analyses followed an electrical neuroimaging approach and were restricted to distracter trials to avoid motor confounds when comparing multisensory and summed unisensory brain responses. The 3x2 ANOVA with factors of category (conspecifics, mammals, birds) and response type (pair/sum) revealed a significant interaction due to nonlinear integration of neural responses (global field power) to conspecifics at ~50ms post-stimulus onset that was not observed for other categories. These results provide the first evidence for facilitated multisensory integration of objects referring to conspecifics.

6. My mind is elsewhere but my nose stays focused: effects of attention and emotion on olfactory perception.

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CISA / E3 / UNIGE[3], Labnic / UNIGE[2], E3 lab / CISA / UNIGE[5], Firmenich S.A.[4], Labnic / CISA / E3 lab /Unige[1]

Odors are powerful emotion elicitors, given their significance and the saliency of their valence. It is known that affectively relevant stimuli can be processed outside of attentional focus. Nevertheless, olfactory emotions are plastic and many cognitive or contextual factors can alter their perception. We therefore investigated whether neural responses to olfactory stimuli are affected by attentional manipulation, using a cross-modal audio-olfactory paradigm.

17 participants were presented simultaneously with odors and sounds. Stimuli were chosen beforehand according to individual preferences during a localizer task, in order to obtain pleasant, neutral, and unpleasant odors (6), and neutral sounds (6). Participants had to perform a categorization task focusing on one or the other modality.

Neural activity in olfactory areas (OFC: orbitofrontal cortex, amygdala, insula) was not enhanced when attention was directed to odors, contrary to auditory areas that were sensitive to the attentional manipulation. Areas associated with valence processing (OFC, insula, pallidum, middle cingulate and temporal pole) were modulated by odor type regardless of the modality of attention. This effect was maintained in right insula and left OFC when the two attentional conditions were tested separately.

These novel results emphasize the unique nature of odors and their emotional quality. The ability of smells to evoke strong affective responses at the brain level, regardless of explicit attention, could reflect some primitive alarm mechanism that detects and signals the presence of potentially harmful malodors, rendering them impervious to attentional modulation, in a comparable fashion to affectively relevant (eg: survival related) stimuli from other sensory modalities.

7. Identification of genes involved in behavioral alterations following stressful experiences

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Individuals subjected to stressful events or fearful experiences during childhood and adolescence are more susceptible to develop psychopathologies such as anxiety and depression disorders later in life. Our laboratory built up a stress paradigm on peripuberty rats, which involves experiences of fearful stimuli in an unpredictable way from P28 to P42. Male Wistar rats subjected to peripuberty stress (PPS) exhibit behavioral alterations in adulthood, such as decreased sociability and increased aggressive behavior. Moreover the PPS paradigm induces changes in gene expression in brain regions that play a key role in the modulation of fear and stress responses, including different amygdala nuclei. Here, we investigated potential changes in the expression of different genes following PPS protocol. We focused our studies in the central nucleus of amygdala (CeA), which has been shown to play an important role in the regulation of social and aggressive behavior, and in hippocampus, structure also involved in the stress pathway. For this purpose, a cohort of male Wistar rats was exposed to the PPS paradigm and their brain was collected at different time points following the end of the protocol. We found that the level of mRNA encoding glucocorticoid receptor (GR) was differently regulated in the CeA and the hippocampus. We also found differential expression in corticotropin-releasing hormone (CRH) and its receptors. Our findings highlight new potential modulators of stress-induced alterations and may eventually lead to new therapeutic approaches for psychopathologies.

8. Does pain smell bad? – Cross-modal anticipatory effects between nociception and olfaction

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Differently from the other sensory modalities, pain is a multi-component stimulus, with both a sensory and an affective-aversive aspects, the latter of which is shared with the experience of olfactory disgust.
We aimed at assessing whether pain expectancy triggers a representation of the somatic properties of the noxious event and/or its affective consequences. We therefore compared for the first time anticipation for two equally-aversive, and yet sensory different, events: thermal pain and olfactory disgust.
We have selected two comparably unpleasant thermal and olfactory stimulations (high/low intensity), which were presented following a pictorial cue. For each kind of stimulation, four different cues were chosen informing about the occurrence of thermal-painful, thermal-painless, olfactory-disgusting and olfactory –non-disgusting events. This yielded to 8 balanced conditions, half of which were consistent (thermal cue followed by thermal stimulation), whereas the remaining half were inconsistent (thermal cue followed by olfactory stimulation). Each trial was structured as follows: pictorial cue, stimulus delivery, and subjective rating of the stimulus.
In line with the literature, we found a significant anticipation effect in consistent thermal trials. Likewise we found a comparable anticipation effect for consistent olfactory trials. Critically, we also found significant anticipation effect when the cue was inconsistent with the stimulation modality (cross-modal effect).
We show in this study that the anticipation of aversive events triggers both a representation of its affective consequences and a representation of the somatic properties of the stimulation.

9. Language specificity of lexical-phonological therapy in bilingual aphasia: a clinical and electrophysiological study

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Based on evidence that bilinguals' first (L1) and second (L2) languages are processed by largely overlapping representations, speech therapy of bilingual aphasic patients non-residing in their place of origin, usually focus only on L2. The benefits of unilingual rehabilitation have been proposed to extend to the untreated languages. However, intra-/cross-language generalization after phonological therapy and the neural bases of this generalization remain unclear.

We examined the transfer from L2 to L1 word production in picture naming tasks (PN) after an intensive lexical-phonological training in L2 in a bilingual aphasic with two distinct languages (Persian and French). The patient suffered from Broca aphasia following left fronto- temporo-parietal- ischemic stroke. Language performance was assessed using PN, Bilingual Aphasia Test (BAT) and word-picture verification (WPV) task. Electroencephalography (EEG) was performed during PN and WPV tasks in both languages before and after the L2 lexical-phonological training on half of the words from the PN task.

Naming of trained items improved after lexical-phonological therapy in the trained L2 but not in the untrained L1. The naming of untrained items did not improve in L2 nor in L1, whereas WPV improved significantly in L1. Topographic analyses of the ERP to the treated L2 words in PN showed a Language*Session interaction driven by changes in the ERP topography to the treated but not to the untreated language at 540ms post-stimulus onset.

These results indicate that the lexical-phonological therapy modified the brain networks engaged in phonological processing during naming only in the trained language for the trained items.

10. The early signal catches the memory: Process differences in rapid consolidation and reality filtering.

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Previous studies demonstrated that evocating memories not pertaining to the ongoing reality ("reality filtering") in healthy subjects triggered a transient desynchronization of the neocortex around 200-300 ms associated to the orbitofrontal cortex (Schnider, 2013). The Spacing Effect, which is the improved retention of items repeated after a delay, suggests similar temporality. James et al. (2009) found that immediate picture repetition induced a positive frontal potential at 200-300 ms emanating from the left medial temporal lobe (MTL). More recently we found this positive frontal potential to be associated with increased theta (3-7.5 Hz) coherence between the MTL and the rest of the brain (Thézé et al., in submission). In this study we addressed the interaction between the orbitrofrontal desynchronization and the MTL synchronization. High-density Electroencephalogram (EEG) was recorded from 18 healthy subjects who performed two runs of a continuous recognition task composed of the same set of pictures, and were requested to indicate picture recurrences within the ongoing run. Pictures were either repeated immediately or after several intervening items. Waveform EEG analysis revealed distinct traces for the two processes between 200-300 ms at the Fz electrode. Also, the electrophysiological changes associated with the processes occurred at significantly distant onset: first immediate repetition then reality filtering. Moreover, spatiotemporal segmentation confirmed the existence of statistically distinct topographies. These findings suggest the two cognitive processes are most likely independently and succinctly occurring in distinct neural circuit within the limbic system. Further investigations are however required to better understand their mutual contribution to memory.

11. Auditory cortex plasticity in patients with unilateral lesions.

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The primary auditory cortex (PAC) is central to human auditory abilities, yet its anatomical location remains unclear. In a previous study with control subjects, we measured two large tonotopic primary subfields, A1 and R, relative to the underlying anatomy of Heschl's gyrus (HG). The size and shape of these subfields are proper to each hemisphere and subject. Here, we speculate that A1 and R could be modulated by events such as stroke or traumatic brain injury. We performed tonotopic mapping in 7 patients and 12 healthy controls at 3T. Progressive cycles of pure tone bursts (from 88 to 8000 Hz in half-octave steps) were presented in blocks of 32 seconds during two 8 minutes runs. PAC was functionally defined as the largest cluster in HG containing the primary mirror-symmetric gradients in each hemisphere and subject. Frequency distributions were calculated as the percentage of the preferred frequency within the total amount of voxels in PAC.

Tonotopic gradients were maintained in ispsi- and contralesional hemispheres, despite some relative alterations in the frequency representations. Frequency distributions were slightly shifted towards the low frequencies in patients with hemispheric lesions, with bigger shift for larger lesions or lesions near PAC. PSC variations per frequency had an ispsilesional drop around 1000 Hz in patients with hemispheric lesions and a contralesional increase in patients with cerebellar lesions. Tonotopic maps were (1) preserved only if primary and non-primary auditory areas were spared by the lesion, and (2) strongly influenced by the distance between PAC and the lesion.

12. Altered modular organization of the brain network at rest in 22q11DS

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The 22q11.2 deletion syndrome (22q11DS) is characterized by cognitive deficits and a high risk of schizophrenia. Alterations of the functional network have already been described in 22q11DS, notably affecting the Default Mode Network (Debbané et al, 2012, Scheiner et al., 2013) and have been identified as a potential biomarker for schizophrenia (Scariati et al., 2014). However, functional graph theoretical analysis is still missing, although this technique provides a unique quantitative analysis of brain organization. Here we study resting-state connectivity in a group of 40 patients with 22q11DS (19F/21M) compared to 41 controls (21F/20M) from 9 to 30 years old (mean age: controls=17.7+/-6; patients=17+/-5). The images were preprocessed using SPM (http://www.fil.ion.ucl.ac.uk/spm/) and parcellated in 90 regions. Connectivity was calculated using a Pearson correlation between the averaged time-series of the 90 regions and a graph theoretical analysis was performed on the resulting network (Brain Connectivity Toolbox, Rubinov and Sporns, 2010). Modularity allows to identify subnetworks, and to measure the degree of segregation between them. We found a significant increase in segregation and a significant difference in subnetworks division, corresponding predominantly to a decreased connectivity between anterior and posterior DMN, what is consistent with the current literature (Scheiner et al., 2013). The increase in segregation may be related to the cognitive deficits of the patients that have difficulties to integrate different kind of information. The decreased DMN connectivity has already been described in schizophrenia and may be related to the presence of psychotic symptoms, what will be tested in future work.

13. Altered light sensitivity in a mouse model for Smith-Magenis syndrome

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Smith-Magenis syndrome (SMS), is a multiple congenital anomalies/mental retardation disorder associated with a deletion on chromosome 17p11.2 or, rarely, with point mutations in a gene located within this deletion, Rai1 (Retinoic acid induced 1). The most constant phenotype in all SMS patients is a circadian misalignment of sleep coupled with an abnormal melatonin rhythm, with maximum melatonin levels during daytime. Since light is known to suppress melatonin, the latter observation suggests an impaired circadian light perception in SMS. RAI1 is believed to be a transcription factor involved in chromatin remodelling and could affect circadian rhythms at a molecular level. We here aim to determine whether an altered circadian time keeping system or problems related to entrainment by light contribute to the SMS phenotype.

We studied circadian rhythms in locomotor activity under light-dark (LD12:12) and constant dark (DD; >20days) conditions in mice heterozygous for Rai1 deletion (Rai1+/-) in C57Bl/6J (B6) and C3H/HeJ (C3H) genetic background. EEG and EMG signals were recorded to evaluate the regulation of sleep.

In B6-Rai1+/- mice, under LD12:12, locomotor activity is strongly suppressed by light ($p<0.001$) while an increased contribution of delta activity to the waking EEG is observed ($p<0.05$). Under DD active phase expanded more in B6-Rai1+/- mice compared to wild type littermate ($p<0.005$). These phenotypes did not occur in C3H background.

B6-Rai1+/- mice present an increased light sensitivity phenotype, with an intension of the light-induced negative masking, but, evinces a drowsy behaviour during the light period similar to the daytime sleepiness described in SMS patients.

14. Spatial working memory deficits in aging: a new perspective.

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Working memory, the memory system that keeps limited amounts of information active for brief periods of time in order to guide behavior, is vulnerable to normal aging processes. Moreover, spatial working memory, essential in daily tasks such as learning new routes or driving, is thought to be especially affected in normal aging. To date, however, the specificity of that deficit has not been unequivocally demonstrated. Indeed, there is no experimental evidence showing, for example, that aging selectively affects spatial working memory rather than spatial processing per se. We tested 10 young (20-30 years) and 11 older (65-75 years) adults in four versions of a real-world memory task requiring participants to learn, on a trial-unique or repeated-trial basis, the locations or colors of three foot-pads among 18 pads distributed in an open-field arena. We found that memory performance was lower in older subjects in all testing conditions. Some performance measures, such as the number of correct choices before erring, suggested that spatial working memory is the memory most affected in aging. However, other measures of memory performance, such as the number of errorless trials, suggested that this deficit may result from the cumulative decline of several cognitive abilities. We propose that because a larger brain network is normally involved in spatial information processing, spatial working memory deficits may appear comparatively larger than non-spatial working memory deficits. Non-pathological age-related declines in spatial working memory might thus be related to functional decline throughout the brain rather than dysfunction of specific brain structures.

15. Limitations of transposing neuropsychological measures to behaviour in a natural environment when assessing fitness to drive in ageing adults

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Compared to younger adults, older adults have reduced vision, more difficulties in detecting relevant information they are not intending to and require more time to process sensorial information. Little is known on how these changes affect behaviour in a natural environment. One such behaviour of interest is that of driving a car – a standardised complex task requiring both lower and higher order cognitive processing skills, for which most people are already trained. Relying on a translational approach at the frontiers between neurobiology, psychophysics, neuropsychology and epidemiology, we were able to measure cerebral decline in healthy older adults and explore the link between processing speed and on-road driving performance. We showed that normal ageing is accompanied by major changes that affect processing speed. These changes nevertheless do not necessarily affect driving performance as they are compensated for at a behavioural level. In consequence, for clinicians, there is no way of perceiving to what extent advanced cerebral decline truly affects driving competency without empirically assessing driving itself. Our work will hopefully contribute to shifting the aims of normal ageing research from trying to explain causes of cerebral decline to exploring mechanisms that will help maintain or recover cognitive functions that older adults need to maintain an active lifestyle.

16. Contributions of chromatic and luminance contrast to illusory contour processing in humans

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The visual system is able to create the perception of boundaries even when the visual input to the retina is discontinuous or incomplete. Kanizsa (1976) popularized commonly used stimuli that are created with a set of circular sectors ('pacmen') that are orientated to induce an Illusory contour (IC) or reversed to create a non contour (NC) condition. An open question concerns the relative contributions of the magnocellular and parvocellular sub-divisions of the visual system to illusory contour processes.

We addressed the extent to which ICs defined by luminance versus chromatic contrast would engage similar brain mechanisms. To do this, we recorded high-density visual evoked potentials (VEPs) from 14 healthy subjects (5 male, all right handed) who viewed Kanizsa-type illusory contours that were either defined by achromatic luminance contrast or isoluminant chromatic contrast, which result in responses biased to the magnocellular and parvocellular sub-divisions of the visual system, respectively. Behaviorarally, The average accuracy in discriminating IC vs. NC stimuli was over 96%. We quantified illusory contour sensitivity as the VEP difference between responses to ICs vs. NCs. This IC sensitivity began ~90ms post-stimulus onset for stimuli defined by chromatic contrast and was phase-shifted ~30ms later for stimuli defined by luminance contrast. Differences were observed in VEP strength, with IC sensitivity defined by chromatic contrast resulting in a stronger response than luminance contrast. The collective results suggest that mechanisms of IC processing may be largely insensitive to the retino-cortical sub-division conveying stimulus information.

17. Impossible Perceptual Learning

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Perceptual learning is learning to see. For example in a bisection task, three parallel lines are presented with the central line slightly offset towards the right or the left outer line. Participants indicate the offset direction. Training gradually improves performance. Models of perceptual learning explain learning by synaptic changes determined by the learning algorithm and the stimulus presentation. In these models, learning cannot occur when the very same stimulus is presented in all training trials. Here we show that, surprisingly, humans can improve performance in such "impossible" conditions. We trained observers with a line bisection task where the central line was always exactly in the middle for all 4160 training trials. Participants were not told about the “zero offset” and were instructed to indicate the offset direction as in a normal bisection task. Surprisingly, performance improved with gains similar to "normal" bisection experiments where both the left and right offset are presented. These results cannot be explained by most of current models of perceptual learning and reproduce previous studies in the auditory domain (Amitay, Irwin & Moore 2006). We suggest that perceptual learning occurs by mental imagery in accordance with previous results (Tartaglia, Bamert, Mast & Herzog, 2009, 2012).

18. Effect of gentle rocking on sleep and memory

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Why do we cradle babies or irresistibly fall asleep in a hammock? In a previous nap study (Bayer et al., 2011), we showed that lying on a slowly rocking bed facilitates sleep onset and strengthens deep sleep with increased spindles and slow wave activity that are known to promote neural plasticity and memory. In the present study, we aimed at assessing the effects of rocking on whole-night sleep and its possible effect on overnight memory consolidation using polysomnography on healthy adults.
Therefore, 19 participants spent two experimental nights in a bed, which either remained in a stationary position or rocked gently at 0.25Hz. To assess memory retention, participants performed a word-pair associate learning task before and after sleep in both conditions. EEG data revealed that rocking increased the duration of deeper sleep (N3) along with increased spindles density and slow wave activity. Memory data analysis showed that rocking yielded a significant increase in the number of word-pairs recalled in the morning ($p=0.004$) as compared to the stationary condition. These findings demonstrate that rocking during a whole night makes us sleep deeper with an increase in spindle density, and that these changes in sleep reinforce memory consolidation processes.

Bayer, L., Constantinescu, I., Perrig, S., Vienne, J., Vidal, P. P., Muhlethaler, M., & Schwartz, S. (2011). Rocking synchronizes brain waves during a short nap. Current Biology, 21(12), 461-462.

19. Behavioral and electophysiological correlates of listening to time-compressed speech.

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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. In this study we employed artificially time-compressed speech to investigate comprehension of rapid speech in a controlled fashion. Behavioral and Electroencephalography (EEG) data were collected from 17 volunteers while they were listening to sentences compressed at different rates. Results revealed that the more compressed the acoustic signal the more difficult it is to comprehend it and this is modulated by previous exposure to this type of distortion. In the EEG data we observed a decrease in power in the alpha band (8-13Hz) as intelligibility decreases, prominent in a central right-lateralized cluster of electrodes, while a more posterior left cluster becomes apparent around 1.5 seconds post-stimulus onset. A similar decrease is observed in the beta band (~15-25Hz) at a small posterior left cluster extending to neighboring sensors one second after the stimulus onset. Future analyses will focus on phase coherence between the acoustic and neural. The existing results replicate previous behavioral findings on time-compressed speech intelligibility and provide insights on the neurophysiological correlates of distorted speech comprehension.

20. Limitations in fine-grained within-category semantic auditory discrimination: insights from spatio-temporal analyses.

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Correct recognition of individual sound objects within a semantic category involves cortical regions along a left lateralized temporo-fronto-parietal network. Here, we investigated how representations environmental sounds, i.e. heartbeats, differ when sounds have been correctly versus incorrectly categorized. EEG and behavioural data were recorded from eleven participants who completed: 1) an audio-visual training session requiring recognition of 4 categories of real patients' heartbeat sounds (the training session ended when participants reached 70% accuracy); and 2) a testing session requiring discrimination of the 4 previously learned categories on recordings of new heartbeat sounds. Accuracy data were analyzed with a one-way ANOVA with Category as factor. There was a main effect of category ($p = 0.033$) that was due to early systolic clicks being the most difficult to recognize. EEG analyses compared correctly vs. incorrectly recognized items with a paired t-test of source estimations calculated for each participant. The results identified a distributed spatio-temporal sequence that included frontal, parietal and occipital areas across separate time-windows. Thus, correct and incorrect recognition of heartbeat sounds relied on distinct brain networks, and these networks involved areas located predominantly outside the auditory brain regions. This pattern of activation differences between correct and incorrect categorization demonstrates that errors in fine-grained discrimination of objects within a semantic category, such as heartbeat sounds, can be driven more by incorrect labeling, rather than by limitations at a lower, i.e. perceptual, processing level.

21. The effects of action video-games on the processing of attended and unattended emotional stimuli

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Research suggests that playing action video games improves attentional control, through an increased ability to ignore distracting stimuli. However, these studies have used exclusively non-emotional stimuli. How is the processing of emotional stimuli modulated by attention in video game players? To examine this question, action video game players (AVGPs) and non-video game players (NVGPs) were compared in an attention-demanding task where they had to detect target faces expressing positive or negative emotions embedded in streams of either neutral or emotional (negative or positive) faces. Participants were required to pay attention to the left or to the right stream (which flickered at different frequencies) and to detect targets only at the attended side. In order to quantify the attention allocated to the attended and unattended streams of stimuli, EEG was recorded and steady state visually evoked potentials (SSVEPs) were extracted and analyzed offline. Preliminary results in 11 AVGPs and 9 NVGPs showed no significant differences between groups in accuracy or reaction time in the detection of emotional targets, whereas neural responses differed between groups. NVGPs showed a larger deployment of attention to the relevant, attended stream compared to AVGPs. No differences between groups were observed in the response to unattended stimuli. These findings contrast with previous studies using non-emotional stimuli and complementary analyses are being done in order to better understand this discrepancy.

22. Differential effects of happy and sad mood on risk taking

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How do we make risky decisions? Typically, people take the risk to gamble if they can win at least twice the amount they can lose. This greater sensitivity to loss than to equivalent gain is called loss aversion. Yet, whether emotional states may influence our decisions remains unknown.
Here, we induced happy or sad emotional state via movie clips and recall of emotional personal episodes. Using fMRI, 24 healthy subjects accepted or rejected monetary gambles with a 50/50 chance to win or lose money (e.g. +22CHF or -10CHF). We found that people accepted more gambles and were faster to answer when being in a happy state compared to a neutral or sad state. As expected, the nucleus accumbens, the ventromedial prefrontal cortex (vmPFC) and the anterior cingulate cortex (ACC), key regions of the reward network, were activated by the task. We found a dorso-ventral segregation along the ACC depending on the mood: when gambling, people in a happy state activated a ventral-affective portion of the ACC, including the vmPFC, whereas in a sad state they activated a more dorsal-cognitive portion of the ACC. Finally, during the happy (vs sad) state, activity of the ventral striatum increased in proportion to the expected value of the gambles.
These results suggests that being happy increased the rewarding value of potential gains and risk taking, while being sad generated a form of cognitive conflict while playing. These findings demonstrate that emotional states modulate decision making and underlying neural processes.

23. Components of epileptic networks show pathological coherent fluctuations even in the absence of scalp spikes

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Background: It has been demonstrated that epileptic activity arises from the dysfunction of a neuronal pathological network (epileptic network) rather than from a single focal source. Simultaneous electroencephalography (EEG)-fMRI can be used to map these networks. The aim of this study was to assess if epileptic networks, revealed by IED-correlated BOLD changes, exhibit coherent fluctuations independently of the occurrence of IEDs on scalp EEG.
Method: We included resting state EEG-fMRI dataset (3T) acquired on seven patients with drug resistant focal epilepsy, having multifocal BOLD response to IEDs and maximal t-value corresponding to the IED field. We excluded patients with epileptic focus in the default mode network. Functional connectivity (FC) was computed from a 10 mm sphere drawn in the region of maximal t-value of the IEDs-related BOLD maps. In a second step, FC was re-computed with IEDs used as confounds. Single subject FC maps with and without removing the effect of the IED were examined and compared.
Results: FC analysis showed a similar epileptic network compared to spike-related BOLD maps. FC maps were largely preserved after regressing out the effect of the scalp IEDs.
Conclusion: Regions involved in a specific epileptic network show functional coupling beyond the occurrence of interictal activity. Beyond supporting the presence of epileptic activity invisible to the scalp, these networks can be seen as pathological intrinsic fluctuations of BOLD signal, in the sense of new or modified RSNs. The interactions between these epilepsy-specific RSNs, the physiological RSNs and behavioral performances remain to be elucidated.

24. Local in vivo exploration of the neurovascular-neurometabolic coupling mechanisms with diffuse reflectance spectroscopy probing in the rat primary somatosensoriel cortex

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Dynamic adjustments to neuronal energy supply in response to synaptic activity are critical steps for the neuronal function. Because the brain lacks energy storage capacity, the monitoring of the local cerebral blood allows the tracking of neuronal activity changes. Consequently, the key question is how the involved cellular ensemble (neurons, astrocytes, endothelial cells) is orchestrated in order to meet the energetic demands related to neuronal activity.
In anesthetized rats, measurements, with an original optical probe providing space and time-resolved diffuse reflectance spectra characterizing small areas of the primary somatosensory cortex (<1 mm3), were made in response to electrical forepaw stimulations. With a mathematical model of photon migration in tissue, the absolute spectra of reduced scattering (RScS) and absorption (AbS) as well as their quantitative changes were calculated. While, RScSs are likely to translate the trans-membrane water movements, the AbSs are related to the vascular responses and the absolute concentrations of the different hemoglobin species.
The astroglial glutamate transporters seem to be a major actor of the vascular response associated to the neuronal activity. The local application of TFB-TBOA (50?M), a non-specific inhibitor of these transporters, on the somatosensoriel cortex induces a 2/3 decrease of the reflectance signal during a 4s stimulation according with previously published data. The analysis of the AbSs shows that TBOA itself increases the local perfusion and saturation. In contrast, the changes of the RScSs seem to be only slightly modulated by TFB-TBOA stressing the occurrence of trans-membrane water fluxes closely link to the neuronal activity.

25. 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. The latter suggests a possible dysfunction in reward-related brain networks. Yet, how BPD patients process evaluative feedback, particularly social feedback, remains poorly understood. We addressed this issue by using event-related functional magnetic resonance imaging (fMRI) in 20 women with BPD and 20 healthy controls (HCs). Participants performed a reward-related task in which cues and feedbacks were either social (neutral faces for cues and happy or angry faces for feedbacks) or non-social (dollar sign and winning or losing money). We hypothesized that BPD patients and HCs process feedback (outcome) differently in limbic/mesolimbic brain regions, especially for social compared to non-social conditions. We observed that, compared to HCs, BPD patients showed a decrease in amygdalae activity for social feedback relative to non-social feedback. And further, BPD patients, compared with HCs, failed to activate the dorsal anterior cingulate cortex (dACC), an area often dedicated to error detection, for situations in which they received a losing social signal compared with a winning one. These findings demonstrate that BPD patients show dampened emotional-limbic reactivity to evaluative social signals. These findings may shed light on why BPD patients suffer from pervasive difficulties in adapting their behavior, particularly in the context of interpersonal relationships.

26. On the impact of 5HT1a receptor on dendritic arborization of hippocampal pyramidal neurons and associated altered behavior

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Focusing on the hippocampus - the region with the highest 5HT1a receptor (5HT1aR) expression in the forebrain - we identified a role for the receptor in regulating dendritic arborization in the stratum radiatum. Constitutive 5HT1a- KO mice show increased secondary branches of pyramidal neurons in the dorsal CA1 region of the hippocampus as compared to wild-type (WT) animals. Furthermore, there is a significant difference between male and female 5HT1aR-KO mice with female showing less secondary branching than males. In our lab we aim at understanding the downstream pathway of the receptor causing increased arborization as well as the impact it has on behavioral levels. In organotypic hippocampal cultures, inhibition of 5HT1aR by selective antagonist or use of KO mice brain resulted in increased dendritic arborization in the stratum radiatum. Interestingly, inhibition of the NR2B subunit reversed the enhanced arborization of 5HT1aR-KO cultures, suggesting that 5HT1aR affects hippocampal arborization through regulation of NR2B. By inhibiting downstream elements of the 5HT1a receptor we aim at understanding the impact of CaMKII and Erk 1/2 within this process.
On a behavioral level 5HT1a receptor KO mice are well known for their increased anxiety-related behavior but other behavioral aspects have only been partly investigated. We therefore are running KO animals of both genders through a battery of behavioral tests focusing amongst others on hippocampal dependent tasks. Gathered results so far hint towards a link between increased amount of arborization and deficits in learning and memory tasks with different motivational value.

27. Acoustic stimulation as a tool for assessing sleep quality in mice

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Well-being depends on good sleep. Sleep quality (SQ) is typically quantified by the amplitude of low-frequency components in the power spectrum of the NREM sleep electroencephalogram, but, in humans, arousal thresholds also serve as measure of SQ. Here, we examined whether arousal through acoustic stimuli reports on SQ in freely-moving C57BL/6J mice chronically implanted for polysomnography (ECoG/EMG).
Acoustic arousal was tested in 4 different SQ conditions: early resting phase (control SQ), late resting phase (lowered SQ), after sleep deprivation (SD, increased SQ) and after injection of a hypnotic (Zolpidem, 10 mg/kg, pharmacologically increased SQ). In all 4 conditions, varying SQ was ascertained via delta-power and sleep architecture measurements. Mice were then exposed to 2 different white-noise protocols (90dB noise pulse for 20s; ramp noise from 60-90dB, 160s). The arousal success rates (ASRs) obtained with noise pulses were lowered for increased SQ (SD, 23.99±4.98%, n=10; early resting phase, 38.74±8.60%, n=10, $p<0.05$; values expressed as mean±SEM), but remained unaltered for decreased SQ in the late resting phase. Similarly, sleep-through rates (STRs) assessed with ramps increased after SD, but not late in the resting phase. Interestingly, in Zolpidem-injected mice, only STRs, but not ASRs reported on increased SQ. Arousal thresholds were not changed in any of the conditions. All noise-induced arousals were preceded by distinct spectral changes. Zolpidem suppressed these specifically during ramp-induced arousals.
Together, noise pulses and ramps differentially reports on changes in SQ and provide insight into the arousal process from natural or pharmacologically induced sleep.

28. Trade-off between spatial resolution and signal sensitivity in functional magnetic resonance studies of deep brain nuclei

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Aim: Despite major progress in the field of high-resolution functional magnetic resonance imaging (fMRI), the reliable and accurate imaging of the iron rich deep brain nuclei neural activity remains challenging. Aim of our study is to find the optimal trade-off between spatial resolution and temporal signal-to-noise ratio (SNR) focusing on subcortical rather than cortical regions. We hypothesized that a 2mm3 resolution would be sufficient in terms of spatial resolution yet not excessively costly in terms of sensitivity, therefore allowing for accurate topology inferences.
Methods: Subjects (n=16) performed in a randomised order three times the same motor execution paradigm involving fingers, toes and lower face movements. Each experimental run has been randomly attributed an EPI acquisition with a specific isotropic resolution – 1.5mm, 2mm and 3mm.
Results: At the group level the EPI sequence at 2mm resolution showed a complete set of somatotopically organized cortical and subcortical areas including primary motor cortex (M1), putamen, ventrolateral nucleus of the thalamus, supplementary motor area (SMA), anterior insula and parietal operculum (OP). 1.5mm and 3mm EPI sequence allowed a full mapping of somatotopy in M1 and the SMA but failed to show significant topology patterns in putamen, insula and OP.
Discussion: Several electrophysiological, tracing and fMRI studies previously showed somatotopic patterns in cortical and subcortical regions reported above. Our results suggest that non-invasive in vivo investigation of fine-grained properties of the human brain motor circuit at 3T is optimized by using a 3D 2mm resolution EPI sequence.

29. Computation based diagnosis reveals intermediate Alzheimer's disease phenotypes

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A definitive diagnosis of Alzheimer's disease (AD) can only be confirmed with pathology. In-vivo clinical criteria alone can lead to 35% misdiagnosis rate. We present a new diagnostic tool for AD based on in-vivo neuroimaging patterns, which predicts pathological proven (PP) AD. We inspected imaging and cognitive patterns from individuals and explored reasons for diagnostic mismatch based on clinical criteria and the results of MR structural neuroimaging based automated classification. We suggest that such individuals have differential patterns of brain atrophy associated with memory loss.

We trained a Support Vector Machine (SVM) on grey matter volume (GMv) estimations from post-mortem proved AD and healthy controls (HC). We relabelled ADNI individuals (clinically diagnosed).

- Training: 15 HC / 18 AD T1-weighted ante-mortem MRI from PP individuals (Klöppel et al, 2008)
- ADNI set: T1-weighted MRI from 359 HC / 284 AD patients (defined by MMSE, CDR scores) at baseline time
- We normalized all GMv images to MNI space using a template generated from PP individuals using SPM12.

SVM classified the 33 PP individuals with 87% accuracy (leave-one-out cross-validation). ADNI individuals were classified either AD or HC and then stratified into 4 subgroups: AD_AD, AD_HC, HC_AD, HC_HC (formatted as clinical_anatomy).

Clinical / neuroimaging mismatch labeled individuals (AD_HC & HC_AD) showed intermediate characteristics in both anatomy patterns and memory performance. This result suggests different mechanisms of clinically AD-type dementia syndrome.

30. Refining cognitive and functional outcome after cardiac arrest

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Improvement of early critical care in patients suffering cardiac arrest (CA) has substantially improved survival rate and more refined measures are necessary to describe their outcome. Our goal is twofold: first, to detail long-term cognitive and functional outcome of CA survivors, and second, to combine this refined outcome with early clinical variables to help predicting functional prognosis.

Survivors after CA treated between July 2012 and October 2013 at our hospital were followed prospectively and evaluated at 6 months using a comprehensive neuropsychological assessment. Cognitive assessment testing 10 cognitive domains categorized patients as cognitively spared (< 2 domains impaired) vs. cognitively impaired (? 2 domains impaired). Functional assessment included quality of life, disability, mood disorders, and activities recovery. Early variables including clinical, biochemical and neurophysiological evaluations were correlated with cognitive and functional measures.

16 CA survivors (11 men; age 57.4 ± 14.7 years) were included. At 6 months, all patients lived independently at home. Cognitively, 25% of patients were classified as impaired. Functionally, 13% reported low quality of life, 6% reported significant mood disorders, and 40% of those previously working did not return to work. Significant correlations were found between serum NSE (a biological marker of acute neuronal death) and processing speed ($r=-0.71$, $p<.01$), as well as between time to awakening from coma and quality of life ($r=-0.52$, $p<.05$).

Detailed characterization of long-term cognitive and functional outcome shows significant impairment in a substantial minority of CA survivors. These measures can be used to help refining early prognostication of long-term functional outcome.

31. Pain coping strategy impacts response in real-time fMRI neurofeedback

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Real-time functional magnetic resonance imaging (rt-fMRI) neurofeedback is an emerging technique that tries to achieve voluntary control of brain regions with beneficial effects in disorders including chronic pain. Previously, little emphasis was put on the influence of personality traits on neurofeedback efficacy and baseline activity. We assessed the influence of pain coping mechanisms during rt-fMRI neurofeedback of heat-induced pain.
28 healthy subjects completed five runs with block-wise painful heat stimulation, four of which included neurofeedback from a pain sensitive area. Pain ratings were obtained after each run and subjects completed the Coping Strategies Questionnaire (CSQ).
Our neuroimaging data suggests an increased activity of higher-level pain-responsive areas including the anterior cingulate cortex (ACC), the caudate nucleus and the left anterior insula for subjects with lower active scores during pain stimulation without feedback. During neurofeedback runs, the active score was correlated with the activity in cognitive brain areas such as the ACC and prefrontal cortex and the hippocampus but also the visual cortex. Additionally, the active score of the CSQ is correlated with pain ratings and mildly correlated with regulation success.
Pain processing in higher-level pain areas seems to be increased in less active copers while active copers might use more elaborate regulation strategies or increased effort during neurofeedback leading to increased activity in visual and higher cognitive areas might, possibly also leading to a higher success rate in pain regulation. Our results demonstrate that personality traits such as the individual coping mechanism influences sensory processing and cognitive control during rtfMRI neurofeedback.

32. Differential patterns of functional and structural neuroplasticity between and within bilateral inferior frontal gyri induced by inhibitory control training

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Ample evidence indicates that inhibitory control, a key executive component referring to the ability to suppress cognitive or motor processes, relies on a right-lateralized fronto-basal brain network. However, whether and how inhibitory control can be improved with training and the underlying neuroplastic mechanism remains largely unresolved.

We used functional and structural magnetic resonance imaging to measure the effects of two weeks of training with a Go/NoGo task specifically designed to improve frontal top-down inhibitory control mechanisms.

The training-induced behavioral improvements were accompanied by a decrease in hemodynamic responses to inhibition trials within the bilateral pars opercularis and triangularis, as well as in the left pars orbitalis of the inferior frontal gyri. Analyses of the microstructural modifications induced by the inhibitory control training revealed increases in grey matter volume and in white matter fractional anisotropy within the right but not the left pars orbitalis and triangularis, respectively. The task-specificity of the effects of training was confirmed by an absence of change in hemodynamic responses to a control working-memory task after the Go/NoGo training.

These collective results indicate that differential patterns of functional and structural plasticity between and within inferior frontal gyri enhanced the speed of top-down inhibition processes and in turn inhibitory control proficiency. They further suggest that training-based interventions might help overcoming the anatomic and functional deficits of inferior frontal gyri manifesting in inhibition-related clinical conditions. More generally, our results demonstrate how parallel investigations of anatomic and functional neuroplasticity enable revealing novel anatomo-functional dissociations within frontal executive brain networks.

33. Although women come from Venus and men from Mars, both desire in the same direction: An original and exploratory eye-tracking study

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Sexual desire can be defined as "an increase in the frequency and intensity of thoughts / fantasies and desire sexual intercourse, desire to interact with each other" (Cacioppo, Bianchi-Demicheli, Frum, Pfaus & Lewis, 2012). It can be triggered by externaland internal stimuli. Few studies have investigated these components of sexual desire.In our investigation, we focused on visual stimuli with the aim of establishing whether or not there exists a specific pattern of visual exploration linked to sexual desire among male and female subjects.
To assess this question, we conducted an eyetracking study in which participants made an esthetic judgment of beauty in addition to a judgment of perceived sexual desire.
Regarding the assessment of perceived sexual desire, the main results for male viewers revealed that they explored longer the breast than the abdomen ($p < .001$) and the genital area ($p < .01$). For female viewers, the pattern of exploration showed that the abdomen ($p < .001$) and the breast ($p < .001$) were scanned more extensively than the genital area. Concerning the differences between male and female viewers, the results revealed that males fixated the genital area more frequently than females ($p = .03$), whereas females trend to fixated more frequently and longer the abdomen than males ($p < .001$), whether they were instructed to evaluate their perceived sexual desire.
Further experiments with patients suffering from hypoactive/hyperactive sexual desire disorders will be conducted in order to determine how pathological conditions may affect perception of sexual cues

34. 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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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 as well as in adulthood. Levels and intensity of 8-oxo-dg (marked for methylated DNA as a result of oxidative stress), parvalbumin interneurons and myeline basic protein will be evaluated with immuno staining.

35. Does reward association lead to better learning? An fMRI study.

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Declarative memory formation engages regions of the medial temporal lobe (MTL; including the hippocampus) as well as of the striatum. Functional interactions between MTL and striatum also enhance memory for rewarded information. Yet, it is unclear whether the 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 effects may transfer from the specific reward cues to semantically related ones, and whether reward value generalization effects influence hippocampus-dependent learning in a subsequent task. Participants underwent a reward conditioning procedure with 2 levels of reward (high-reward, low-reward) respectively associated with images from 2 distinct semantic categories. Next, they performed a spatial memory task with the same HR and LR images, as well as with new semantically related images.

We found evidence of carry-over effects of reward association in the learning task and at delayed test 24h later. First, the amygdala reward anticipation response during conditioning was positively correlated with performance accuracy for HR pictures early during learning. Furthermore, comparing correct to incorrect recall of HR pictures showed the strongest activation in the striatum. Intriguingly, we found that high trait reward responsiveness was associated with poorer memory for reward-associated pictures 24h later. Finally, we found evidence for generalization of the reward association in better source memory for pictures directly and indirectly associated with reward.

These preliminary findings provide some evidence for a lasting influence of reward association on subsequent memory formation.

36. The medial temporal lobe structures: neuronal representations of memory and effective connectivity with frontal cortex

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The Medial Temporal Lobe (MTL) is composed of structures having an essential role in declarative memory. Regional atrophy in MTL and memory dysfunction are hallmarks of Alzheimer's disease, but there is still poor understanding of the structural mapping of memory processes in the MTL and the connected cortical regions. In our study, we used two paradigms with functional MRI: the "remember-know" paradigm (Experiment 1) to differentiate between recollection and familiarity components in the MTL; and secondly (Experiment 2), a "Multiple Cues Probabilistic Learning" (MCPL) paradigm, to probe the interaction between different memory systems.

In experiment 1, we used high-resolution fMRI (7T) and a Multivariate Bayes approach to test whether MTL structures, namely the hippocampus, parahippocampal cortex and perirhinal cortex, contribute to a unique declarative memory process or if they are associated with distinct memory functions. We demonstrated a dissociated neural representation, with different sparsity level, in segregated MTL subregions for recollection.

In experiment 2, we analyzed subject's learning with dynamic logistic regression method and included it in group level fMRI analysis. Concomitant activation in MTL and in basal ganglia suggests a cross-talk between the episodic and procedural memories as well as a left posterior occipito-temporal activation specific for perceptual/priming memory. Dynamical causal models showed that online cue integration is driven by prediction error reduction within higher hierarchical cortical regions.

To conclude, our results provide new insight on anatomic-functional mapping of memory and learning in the MTL structures and on the role of bottom-up and top-down influences on memory systems.

37. Reading Strategies Across Languages In Early And Late Bilinguals: An Eye-Movement Study

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Reading strategies vary across languages, notably at the level of eye movement patterns during reading. Different eye-movement patterns have indeed been observed when reading transparent (simple grapheme/phoneme conversions) and opaque languages (complex conversion). We recently showed different reading strategies between a transparent (German) and an opaque (French) language in the same early bilingual individuals, suggesting that a local reading strategy (first fixation location close to the beginning of words) for transparent languages, and a more global reading strategy for opaque languages (first fixation location less close to the beginning of words). In the present study, we aimed at i) confirming the results of our first study with late bilinguals; and ii) examining how much the reading strategy of the second language is influenced by language opacity. We assessed two groups of late bilinguals, one with French and the second with German as mother tong (L1). The procedure was the same as for the study on early bilinguals: the late bilinguals were instructed to read aloud isolated French and German words and pseudo-words while the landing position of the First Fixation Location (FFL) was measured. Preliminary results suggest that as compared to the early bilingual group, late bilinguals with German as L1 engage a more local reading strategy for the transparent German context. These results suggest that when highly proficient, early bilinguals read different languages, they do so as would do monolingual in each of the language.

38. Contrast-Polarity Dependent Temporal Perceptual Decision Making And Pharmacologic Insights Into Delay- And Effort-Based Cost-Benefit Decision Making

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UniFr

The work to be presented is comprised of two parts. In the first part of the study, we studied the temporal characteristics of visual perception in human and tree shrew subjects. We used 3 alternative force choice tasks using three visual stimuli in which only the target stimulus was flickering with two iso-luminant distractors. The flickering stimulus could differ in three factors including flicker frequency, contrast modulation depth and contrast modulation polarity (i.e. increment or decrement). We found that in both tree shrews and humans, the subjects exhibited higher sensitivity to contrast decrements compared to contrast increments. Neuronal recording from the anesthetized tree shrews V1 supported the behavioral findings such that majority of neurons responded more strongly to contrast decrements.
In the second part of this study, we trained rats to perform delay- and effort-based T-maze decision making task and tested their behavior following activation of cannabinoid type 1 receptor in either orbitofrontal cortex (OFC) in rats performing delay-based or anterior cingulate cortex (ACC) in rats performing effort-based decision tasks. We found that local cannabinoid activation in the OFC and ACC shifted the rats preference from high reward-high cost choices to low reward-low cost choices. A variety of control experiments ensured that the effects are resulted from changes in decision processing and not spatial or reward memory confounds. Immunohistochemistry experiments implicated the involvement of mostly GABAergic interneurons but also to a lesser degree other neuronal populations. Taken together, these set of experiments suggests cannabinoid receptor type 1 as a major player in decision making circuits.

39. Investigation of Contrast Sources In T1w MR Protocols.

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Voxel- and surface- based techniques rely on a range of *T*1-w MRI protocols. These imaging methods provide high spatial resolution and good tissue contrast, which explains their wide usage in clinical radiology and research. In a conventional T1-w image, the signal is not exclusively dependent on T1 contrast but also on other MR parameters like proton density (PD) and T2*; each of them reflects a particular microstructural tissue property. Computational neuroanatomy makes use of T1-w data to estimate grey matter (GM) volumes and employees the estimates in mass statistics to discover possible structural differences among groups of subjects. The volumetric differences can be due to either structural atrophy, or image contrast reduction caused by tissue property changes.
In order to disentangle anatomical changes from microstructural ones, we want to analyze the MR parameters effects on T1-w image contrast and subsequently on the GM volume estimation using a whole brain approach. To this end we use quantitative multi-parameter MR protocol in order to create synthetic T1-w images by applying the analytical formula of the state of the art protocol. The synthetic images allow switching on and off the contribution of different MR parameters to the MR signal. We then employ statistical test to compare the GM volumes estimated from T1w images, created using different MR parameters. As each MR parameter reflects a different tissue property, such as myelin, iron and water protons content, we can correlate the GM volume changes with the contribution of different tissue properties to the image contrast.

Computational Neuroscience

40. Neurostructural correlates of aphasia in acute stroke: a VBM analysis of quantitative native CT scans

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OBJECTIVES/BACKGROUND: Previous studies have shown that neuroimaging can enhance our knowledge about stroke patients' language recovery. Currently, accurate prediction of patients' outcome and rehabilitative strategies was based on inferences from magnetic resonance imaging studies (MRI), which are not always possible to carry out in the clinical routine. Here, we investigate how native Computed Tomography (CT) scans acquired in the acute ischemia stage can be used to find the relationships between brain anatomy and aphasia in the framework of Voxel-Based Morphometry. We also show how CT, a quantitative measure, can be used to detect lesions in an early stage of the disease.
METHOD: We collected data from 84 subjects including whole-brain CT-scans and bed-side clinical assessment from board-certified neurologist. We grouped the patients according to the presence or absence of speech impairment and correlated it with local Grey Matter (GM) volume.
RESULTS: We demonstrated that the regions which present a loss of GM overlap with areas involved in language processing. We analyzed at the voxel level intra-individually CT intensities inside and outside the lesion and identified quantitative cut-offs for lesion detection in white and grey matter.
CONCLUSION: Native CT scans performed in the acute stage of stroke provide robust and accurate information about the location of brain lesions and their relationship with aphasia. CT data give specific lesion features which differentiate both in time and tissue characteristics from other MRI modalities. This can further lead to integrated multimodal analysis of behavior and brain anatomy after ischemic stroke.

Development

41.The 5-HT6R controls pyramidal neuron migration

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The coordinated migration of different subtypes of excitatory neurons into specific layers is key in the assembly and subsequent function of cortical microcircuits. Work in the field has shown that the cyclin-dependent kinase 5 (Cdk5) is a master regulator of pyramidal neuron migration. Interestingly we find that the serotonin 6 G protein-coupled receptor (GPCR) binds to Cdk5. In this work we provide evidence that the serotonin 6 receptor plays a critical in the positioning and migration of pyramidal neurons during mouse corticogenesis. Collected data indicates that constitutive expression of the 5-HT6R controls pyramidal neuron migration through an agonist-independent mechanism that requires cyclin-dependent kinase 5 activity. Taken together these data support an in vivo role of constitutive activity at a GPCR for neocortical radial migration.

42. Manipulation of early activity in migrating cortical interneurons

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Electrical activity has been shown to control the migration of a specific subtype of cortical INs arising from the caudal ganglionic eminence (CGE), opening the possibility that neurotransmitters could regulate this process. CGE-derived interneurons (cINs) specifically express the 5-HT3A receptor (5-HT3AR) while they migrate from the subpallium into the dorsal pallium. Previous work in the lab indicates that 5-HT3AR activation regulates the migration of cINs while they invade the cortical plate. We investigated the role of activity and 5-HTRAR-mediated activation in the generation of calcium transients in migrating cINs. In vitro, we find that 5-HT3AR activation reliably triggers calcium transients and that activity and NMDA /AMPA receptors are not required in this process. In cortical slices, we find that 5-HT3AR activation significantly increases the frequency of calcium transients in migrating interneuron while they invade the cortical plate but not during the earlier process of tangential migration. In cortical slices 5-HT3AR-induced calcium transients required activity and functional NMDA/AMPA receptors. To directly manipulate activity in cINs, we overexpressed ChR2 in cINs migrating in cortical slices. We found that ChR2-induced changes in the frequency of calcium transients increased the pausing time of migrating cINs, suggesting that calcium transients could code for the termination of migration. 5-HT3AR-induced calcium transients were found to require functional L-type voltage-gated calcium channels. Current studies are focused on determining the role of the L-type CACNA1C subtype on the migration of 5-HT3AR-expressing interneurons using genetic approaches. These results give new insights on the mechanisms that mediate the effects of 5-HT3AR activation on the migration of cortical interneuron subtypes.

43. Investigating down-stream genes regulating the migration of CGE-derived interneurons

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Interneurons (INs) account for about 20% of the neuronal population in the neocortex and are crucial to establish inhibitory modulation in cortical microcircuits. INs arise from micro-regions of the subpallium, specifically the medial and caudal ganglionic eminences (MGE and CGE respectively) and the preoptic area. The ionotropic serotonin receptor 3A (5-HT3aR) is specifically expressed in CGE-derived INs (cINs) and our previous work indicates that this receptor regulates the migration of cINs into the cortical plate (CP). In this study, we aimed to identify down-stream molecular targets of the 5-HT3aR and investigate their function during CP invasion. At this end, a microarray screen was preformed at three different developmental time-points on FACS-isolated cINs in wildtype and 5-HT3aR-ko mice. Analysis highlighted the guidance receptor PlexinA4 (PlxA4) as a candidate gene specifically dysregulated in 5-HT3aR-ko cINs as they invade the CP. Using loss-of-function approaches on cortical slices, CGE-targeted in utero electroporation and knockout mice, we are currently determining whether PlxA4 and its possible ligands regulate the migration of cINs into the developing cortex.

44. Investigating the interaction between the 5-HT3AR and early-life stress on cortical microcircuit development

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In humans early-life stress (ELS) interacts with serotonin-related genes such as the serotonin receptor 3 (5-HT3AR) to increase risk to stress-related disorders. Data from the lab indicates that ELS significantly impacts the methylation status of the promoter region of the human 5-HT3AR in an allele-specific manner. Mice models are needed to investigate ELS/5-HT3AR interactions on neural circuit development. Interestingly data from our lab indicates that the 5-HT3AR is specifically expressed in a subset of cortical interneurons (INs) derived from the caudal ganglionic eminence (CGE). In this project we propose to determine whether the 5-HT3AR regulates the functional integration of CGE-derived INs in cortical microcircuits. We propose to use 5-HT3AR-ko mice and conditional shRNA cre/lox strategies in interneuron-specific CGE reporter mice lines to specifically knock-down expression of the 5-HT3AR in CGE-derived INs during the phase of functional synaptic integration. Axonal and dendritic tracing, electrophysiology and synaptic markers will be used to assess the impact of 5-HT3AR loss-of-function on the integration of CGE-derived INs in cortical microcircuits. To study the ELS/5-HT3AR interactions at a molecular and behavioural level we will employ a perinatal stress protocol in collaboration with the Sandi lab in control and 5-HT3AR-ko mice. Mice will be assessed using a battery of behavioural tests probing social and emotional domains in order to determine whether the 5-HT3AR is required in modulating ELS-induced stress-related behaviors. Furthermore, RNA sequencing and methylation analysis will be performed in order to identify key ELS-induced target genes that are under the control of the 5-HT3AR.

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

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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 Tomato-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 ?m 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.

46. Developing tools and approaches to study GABAergic synaptogenesis in the cerebral cortex during the early postnatal period

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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. We are currently using two separate approaches for detecting the clusters: 1) immunostaining against endogenous gephyrin and 2) in utero electroporation of fluorescently tagged gephyrin.
Electroporating rat pups on the embryonic day E17.5 labels cortical layer 2/3 neurons with the plasmid of our choise. 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 puncta 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, after various treatments at different developmental stages.
As a conclusion, with the technique we created, it is now possible to study GABAergic synapses on single pyramidal neurons, in quantities unmatched by those achieved by electron microscopy or any other methods available.

47. Investigating the role of cell-intrinsic activity in somatosensory circuit formation

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Mature neuronal circuits arise from the coordinated interplay of cell-intrinsic differentiation programs, target-derived signals and activity-dependent transcriptional programs. While cell-intrinsic mechanisms predominate at early stages of differentiation, neuronal activity modulates circuit formation at later stages of development. The whisker barrel cortex is particularly well suited to study this latter issue. During the first few days after birth, thalamocortical axon (TCA) arbors from the ventral posteromedial nucleus (VPM) form synapses with layer IV spiny stellate neurons, which aggregate to form barrels. The spatial barrel pattern reproduces the distribution of the whiskers on the snout of mice and its establishment depends on the information coming from whisker activation.
There is a well-established time window that goes from postnatal day (P) 0 up to P4, during which structural alterations occur upon input deprivation. During these first few days after birth, damage to the sensory periphery impairs TCA patterning, while lesions after this period have less pronounced effects. However the role of TCA postsynaptic partners, layer IV Spiny stellate neurons, in the patterning of somatosensory circuits is still unclear.
Here we selectively control spiny stellate neuron activity using gain- and loss-of-function approaches in vivo to investigate the activity-dependent control over barrel cortex formation during development. Together, these experiments aim to address the role of postsynaptic neurons in the developmental assembly of thalamocortical circuits.

48. Integration of grafted neuronal progenitors into the neonatal cerebral cortex following induced neuronal apoptosis.

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Early brain injury after perinatal insults such as hypoxic-ischemic injury, could lead to the devastating sequels like cerebral palsy, epilepsy and mental retardation. The core feature of these lesions is the massive cell death of various cell types. Neural progenitor cell (NPC) based approaches hold promises for compensating the neuronal loss. However the efficiency of these approaches for neuronal replacement in vivo remains yet very limited and little is known about integration of grafted cells into the host circuits. Here we studied the integration of grafted neuronal precursors in the intact and lesioned neocortex. We took advantage of a new, highly reproducible model of neuronal ablation utilizing a diphtheria toxin/diphtheria toxin receptor system to induce synchronized apoptotic death of the layer II neurons in the rat somatosensory cortex at P15 (the period of activity-dependent plasticity). Transplantation of embryonic layer II progenitors was carried 5 days later. Analysis of transplanted grafts was performed at day 7, 14 and 30 after transplantation. Our preliminary results indicate long survival (up to 180 days) and good tissue integration of transplanted cells, that typically remain in cluster. We found that neurons in cluster are engaged in synaptically interconnected network. The donor cell cluster sends out numerous outgrowths to the host tissue and receives innervation from the cortex. Moreover, the lesion environment promotes maturation of transplanted progenitors resulting in the increased complexity of their dendritic arbors. The model provides new possibilities for exploring the integration of transplanted cells into preexisting network following injury.

49. Postnatal positioning of neuronal precursors in the neocortex: the role of Wnt signaling pathway

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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 evaluated the role of canonical Wnt signaling during cell migration. We developed a set of molecular tools and introduced them in vivo into proliferative cells of the developing cortex via in utero electroporation. Using a reporter construct for a destabilized GFP variant under the control of beta-catenin responsive promoter (TOPdGFP), we found that the Wnt/beta-catenin signaling is active in postnatally migrating pyramidal cells. In particular, we found that cells in the ventricular zone and lower subventricular zone (SVZ) expressed high levels of dGFP. In contrast, in the upper SVZ where multipolar cells are known to gain a bipolar morphology and initiate radial migration, we observed a reduced GFP fluorescence activity. These cells re-express higher level of dGFP in the intermediate zone (IZ) and cortical plate (CP). Overexpression of Wnt3a, a canonical signaling ligand, or of beta-catenin altered cell morphology. Moreover cell movement was significantly delayed into the upper IZ and CP. Furthermore a dominant negative construct for TCF4 altered radial glia guided locomotion and induced significant delay in migration into the CP. These findings demonstrate that different activity levels of Wnt/beta-catenin signaling are essential for specific stages of pyramidal cell migration.

50. The role of K-Cl cotransporter KCC2 in the development of pyramidal neurons in the cerebral cortex

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For normal brain functioning, a precise balance in excitation and inhibition between neural circuits is required. The neuron-specific potassium-chloride cotransporter KCC2 has an important role during the maturation of inhibitory GABAergic neurotransmission by controlling Cl- homeostasis. Importantly, KCC2 is detected form early stages of brain development, evidences from recent studies suggest, that KCC2 has other function during development besides its transporter characteristic. The recently revealed interaction with the cytoskeleton opened the line of reports describing its involvement in processes unrelated to Cl- transport. In line with these observations, we investigated the putative morphogenic role of KCC2 in the development of cortical pyramidal neurons. To this aim, I took advantage of in utero electroporation to express a small interfering hairpin RNA silencing KCC2 (shKCC2) at embryonic day 17.5 in precursors of layer II/III pyramidal neurons in the rat somatosensory cortex. Using these techniques, I studied the role of KCC2 in the proliferation, migration and differentiation of these principal cells. I found no difference in cell proliferation and early apoptosis between control and shKCC2-electroporated animals. However, examination of early differentiation markers showed a decreased number of progenitors in the shKCC2 electroporated brains compared to controls. The shKCC2 electroporated cells showed disturbed intracortical distribution pattern. Time-lapse imaging of cortical slices revealed an impaired migration speed of these cells. shKCC2 containing neurons arriving to layer II/III demonstrated a highly perturbed dendritic spine morphology and density compared to controls. In summary, these results indicate that KCC2 is required for the normal development of pyramidal neurons.

51. Retinal Ganglion Cells differentiation and energy metabolism

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Glycolysis has been associated with proliferating progenitors, while differentiated cells rely mainly on oxidative phosphorylation for energy supply. It is unknown how the switch from glycolysis to oxidative phosphorylation is related to the onset of differentiation. In the developing retina, the first neurons specified are the Retinal Ganglion Cells (RGCs) that project axons to the brain. Live-imaging of the retinal epithelium has revealed that, after their ultimate mitosis, the siblings are immobilized on the apical surface for about 15 hrs and extend their axon before they migrate to their final location on the basal surface. To determine whether immobilization close to the subretinal space and the retinal pigmented epithelium reflects a need in energy supply, we tracked mitochondria distribution in newborn RGCs, and found that mitochondria accumulate in the apical processes. During migration to the basal surface, mitochondria are relocated in the soma before they move in growing axons. To track biogenesis of mitochondria during the conversion of progenitor to RGCs, embryonic retinas were electroporated with stage-specific reporter plasmids and cells were dissociated and sorted by FACS. The large majority of cells that up-regulate Atoh7, a transcription factor required for RGC production, contains mitochondria. In contrast, mitochondria were not detected in uncommitted proliferating progenitor. As mt-DNA is proportional to the total mitochondrion volume, assessing the amount of mt-DNA in those populations by qPCR will enable us to quantify precisely mitochondria during RGC differentiation, and confirm the link between mitochondria biogenesis and transition from competent progenitors to committed RGCs.

52. Voice perception in premature and full term newborns using high-density EEG and fMRI.

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Hearing in the fetus is already functional during last months of pregnancy and shortly after birth, full-term neonates already demonstrate a preference for their mother's voice. After premature birth, the immature brain is exposed to various auditory stimulations and the question if preterm babies benefit of these early sensory experiences remains open.?

The aim of this EEG and fMRI study is to investigate the neural pathways involved in voice perception in full-term and preterm infants tested at term equivalent age (TEA).?

Functional MRI (Siemens 3T) and high-density EEG (Geodesics, 109-channel) were performed on 21 full-term and 33 preterm newborns at TEA while listening to their mother's voice and an unknown voice. ?

A two-sampled t-test was performed to compare the two groups of newborns and we obtained significant activation ($p<0.005$) for the comparison between mother and stranger voices in posterior part of left superior temporal gyrus, bilateral prefrontal cortex and posterior cingulate gyrus. The ERP results showed significant differences between the two voices ($p<0.05$) on temporal and anterior electrodes in both group, but the topographic maps revealed more pronounced differences in the full-term group.?

These results on both fMRI and EEG studies, show concordant effects of voice processing in newborns. The difference in cerebral processing between the mother and stranger voices is coherent with previous studies in 2months old infants. Preterm babies are tested at TEA, so with 2-3 months of postnatal sound exposure. Thus, early ex-utero experiences could influence the maturation of the auditory network and speech processing.

53. Music processing in newborn assessed by fMRI

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Few days after birth, full-term newborns show predominantly right-hemispheric activations in auditory cortex when listening to music. Furthermore, discriminative response to pitch seems to be already present in 2 months old children. The aim of this study is to understand how music is processed in preterm and full-term newborns and to see to what extend preterm infants could benefit from early auditory experience.?
28 healthy newborns (15 preterm scanned at term equivalent age (TEA) and 13 full-term infants) have been recruited. Infants underwent functional MRI (fMRI) at 3T without any sedation. FMRI data were realigned; coregistered; normalized to a T2 neonatal template; and smoothed. Random-effect analyses have been done to observe the group activation on all newborns and to compare term and preterm newborns.?
At the group level, we observed bilateral activation of auditory regions. At the cluster level, the right auditory cortex was more activated than the left auditory cortex during music compared to silence condition. Furthermore, preterm infants exhibited more activation in the superior parietal lobule when listening to original music than transposed melody. ?
Even if music processing similar to what is found in adults, with functional asymmetry in auditory cortex, is already present in full-term and preterm infants at TEA, an adult like processing of transposed music is more present in preterm infants at TEA than in full-term newborns. Preterm newborns are tested few months after birth, thus, they may have benefitted from this early postnatal auditory exposure.

54. Estrogen modulates CA1 pyramidal morphology through NR2B NMDA subunit: its contribution in the female 5HT1A-deficient mouse phenotype.

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5HT1a-deficient mice display anxious-like behavior during adult life. CA1 pyramidal neurons (CA1-PN), with highest 5HT1A receptor (Htr1a) expression in the forebrain, show exuberant oblique dendrite growth and NR2B subunit overexpression. We have analyzed GFP expressing CA1-PN dendrites in developmental series of WT and 5HT1a-deficient (KO) mice from P10-P60. Interestingly, dendritic exuberance in adult occurs only in male KO mice. In female KO mice, dendritic arborization reduces to WT values at puberty (~P25). Our working hypothesis is that estrogen receptors (ERs) contribute to the morphologic phenotype observed in the Htr1aKO female mice and could interact with NR2B.

Estrogen modulates dendritic growth of CA1-PN in vitro in organotypic slices. This modulation occurs via activation of GPR30, a specific estrogen receptor coupled to a G-protein. Coupling of GRP30 activation to NR2B via DAPK1 and its regulation of dendritic growth is tested in vitro by blocking DAPK1 phosphorylation. Moreover, neonatal GPR30 agonist injection in KO male reduced the dendritic morphology. Testosterone, an alternative source of estrogen via CYP19, has been evaluated in vitro and in vivo. Electrophysiological recording in hippocampal slices confirmed increased NR2B component in NMDA responses of 5HT1a-deficient mice, and showed altered plasticity at Shaffer Collateral synapses with enhanced potentiation after 5 Hz stimulation.

Our current data suggest that estrogen rise occurring first at puberty in females compensates in vivo the exuberance of CA1 oblique dendrites of 5-HT1a-deficient mice by interacting with NR2B to modulate the morphology and function of this hippocampal circuit.

55. Effects of altered expression of SynCAM1, Neuroligin-1B and Neuroligin-2A on adult-born neuron integration and survival

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Hippocampal adult neurogenesis results in the formation of new neurons in the adult hippocampus and participates to learning. The maturation and survival of new neurons is regulated by their activity during the first month after division. Here, we tested whether enhancing synaptogenesis may increase new neurons' survival and maturation during this critical developmental phase.

We tested the effect on the integration and survival of three cell adhesion molecules, SynCAM1, Neuroligin-1B (NL1B) and Neuroligin-2A (NL2A). SynCAM1 is known to increase excitatory synaptic efficiency, whereas NL1B increases the formation of excitatory synapses. NL2A increases the formation of both excitatory and inhibitory synapses. We used a viral-mediated cell specific gene delivery approach to selectively overexpress SynCAM1, SynCAM1 dominant negative isoform (dnSynCAM1), NL1B or NL2A in adult-born hippocampal neurons in wild-type mice. We then assessed changes in neuronal survival and maturation.

SynCAM1 increased dendritic spine maturation, whereas NL2A and NL1B increased dendritic spine formation. dnSynCAM1 induced the opposite effects as SynCAM1 on spine maturation. The overexpression of SynCAM1 and NL1B had no effect on neuronal survival, whereas the overexpression of dnSynCAM1 decreased neuronal survival, suggesting that the maturation of excitatory synapses is crucial for adult-born neuron survival, but that enhancing the formation or the maturation of excitatory synapses is not sufficient to increase neuronal survival. The overexpression of NL2A increased neuronal survival, suggesting that inhibitory synaptogenesis is crucial for neuronal survival.

56. Regulation of axonal path-finding in recently evolved olfactory circuits

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The way in which novel neural circuits emerge during evolution is an important, yet poorly understood biological 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 represent recently evolved neural pathways. During evolution, IR75a, IR75b and IR75c have segregated their expression into three distinct olfactory sensory neuron populations that project their axons to different, but adjacent, glomeruli. Here we aim at unraveling the molecular mechanisms underlying these subtle targeting differences that gave rise to these three segregated olfactory circuits. To that end, we are performing high-throughput gene expression analysis of IR75a, IR75b and IR75c expressing olfactory sensory neurons. In a first approach, we manually isolate genetically GFP labeled OSNs from each subpopulation, and subsequently perform a transcriptome analysis by next-generation sequencing (RNA-Seq). In a second approach, a genome-wide profiling of each of these three neuronal population is achieved using a targeted DNA adenine methyltransferase identification (DamID) technique. Here we present preliminary results from both of these methods, and show that both of them allow the identification of putative axon guidance molecules responsible for the differential wiring of IR75a, IR75b and IR75c expressing neurons. In the future, the most promising candidates will be analysed by 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 of neural circuits and their evolution.

57. Impact of early-life serotonin dysregulation on the development of 5HT3AR+ cortical interneurons

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In humans, monkeys and rodents early-life stress interacts with the serotoninergic system to increase risk to stress-related phenotypes. Studies in rodents reveal that early-life serotonin dysregulation may affect cellular processes involved in cortical circuit formation. A target of serotonin, the serotonin receptor 3A, is specifically expressed in caudal ganglionic eminence derived cortical interneurons (cINs) and this receptor controls cINs migration. We studied the impact of early-life serotonin dysregulation on the molecular programs controlling migration and development of cINs. Using fluorescent-assisted cell sorting (FACS) of cINs and microarrays, we identify a set of common genes dysregulated in migrating cINs in mice genetically deleted for the serotonin transporter (SERT-ko) and mice exposed to a selective serotonin reuptake inhibitor (fluoxetine-exposed) during pregnancy. Using time-lapse imaging, the migratory speed of cINs is specifically increased in marginal zone of SERT-ko mice and fluoxetine-exposed mice. At later postnatal time-points (P21) the positioning of a specific subset of cINs (VIP+ INs) is specifically altered in cortical superficial layers of SERT-ko mice and fluoxetine-exposed mice. The distribution of MGE-derived INs and other subclasses of cINs are not altered. Using qPCR, we find that exposure to fluoxetine altered the expression pattern of VIP in the developing cortex. The dendritic morphology of VIP+ cINs is also altered. These data indicate that in models of early-life serotonin dysregulation, migration and molecular programs of migrating cINs are altered, specifically VIP+ interneuron subtypes in superficial cortical layers. These data add to the growing evidence that early-life serotonin dysregulation impacts on cortical microcircuit formation.

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

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Using in vivo cell-type specific manipulation of pyramidal neurons progenitors, we 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, and codes for an adhesion protein expressed during cortical development. Interestingly whole exome sequencing revealed a de novo DGCR2 mutation in an idiopathic schizophrenic patient. Here we show that shRNA mediated down-regulation of the expression of mouse (m)DGCR2 during corticogenesis dramatically affects the laminar positioning of PNs at postnatal day 0 and 7 is in 2 brain regions: the somatosensory cortex and the medial prefrontal cortex. DGCR2-shRNA-induced mispositioning is fully rescued by overexpressing the human (h)DGCR2 which is not targeted by the mDGCR2-shRNA. In contrast, hDGCR2 containing the de novo mutation is not able to fully rescue the DGCR2-shRNA-induced mispositioning, indicating a functional role for this mutation. In order to further understand the biological function of DGCR2, we will investigate the role of specific DGCR2 domains and identify potential binding partners. Finally we intend to study the behavioural consequences of prefrontal cortex shRNA-DGCR2 alterations during development. These studies will allow us to understand the role of DGCR2 in cortical circuit assembly and study the impact of specific prefrontal cortex microcircuit developmental alterations on the emergence of schizophrenia-related phenotypes.

59. Dissecting cellular diversity during corticogenesis

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Although recent progress has been made in identifying functional genes that distinguish the distinct subtypes of neocortical neurons, the transcriptional programs that specify post-mitotic neurons upon birth from a progenitors remains unknown. Identifying these initial specification programs is critical, because they set the stage for the subsequent differentiation of these neurons and underlie their diversity, which underlies cortical function.
Building on previous work from the laboratory, we investigate the molecular diversity of cortical neurons during development. Identification of transcriptional and input-dependent programs that. Identification of transcriptional and input-dependent programs that control the early differentiation of cortical neurons will provide a precious resource to investigate gene-function relationship during differentiation of neocortical neurons, and pave the way for future
investigations of their function.

Molecular and Cellular Neuroscience

60. Phosphorylation of MAPK2 and MAPK3 regulates sleep

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Introduction: Sleep is a complex behaviour and its functions and molecular pathways remain elusive. Evidence suggests that sleep occurs at a cellular level with predictive changes in gene expression. Nevertheless, how wakefulness and sleep triggers molecular changes is largely unknown.
Methods: To study and understand the molecular pathways of sleep, we used a model of sleep in vitro (Hinard et al., 2012). In this study we investigated the effect of MAPK2 and MAPK3 phosphorylation on the transcriptional markers of sleep. For this purpose, we used an inhibitor of MAPK phosphorylation (U0126) in our primary cortical cultures and assessed gene expression. Additionally, the same inhibitor was directly perfused in the lateral ventricle of mice during 7 days and vigilance states were assessed.
Results: In vitro: when cultures were pre-treated with U0126 transcriptional correlates of sleep were largely inhibited. In vivo: preliminary results suggested that MAPK1 and MAPK2 are quickly phosphorylated during wakefulness (less than twenty minutes). Inhibitor of MAPK phosphorylation reduced NREM sleep duration but both NREM and wakefulness were more consolidated.
Conclusion: MAPK pathway could be the missing link between the vigilance states and the underlying changes in gene transcription.
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61. In vitro generation of dynorphin, NARP, and MCH expressing neurons from mouse fibroblasts

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Introduction: The sleep disorder narcolepsy is characterized by excessive daytime sleepiness, sleep attacks, cataplexy, hypnagogic hallucinations, and sleep paralysis. Loss of orexin, dynorphin and NARP peptides within the lateral hypothalamus is well established in the brain of narcolepsy patients. In the present project taking advantage of induced pluripotent stem cell techniques we are aiming at producing neurons expressing lateral hypothalamic markers including NARP, Dynorphin and orexin to test their physiological properties in-vitro.
Methods: Neuronal differentiation was carried out using embryonic body (EB) formation method from embryonic mouse fibroblasts.
Results: The iPS cells were established and were characterized. There is only one report about differentiation of embryonic stem cells toward hypothalamic progenitor cells (1). Using modified version of this protocol, in preliminary studies, coaxing iPSC lines toward hypothalamic progenitors resulted in expression of hypothalamic genes Rax, Six3, and Vax1. We observed the expression of lhx9 in all SHH treatments and lhx6 gene in 10, 30, 50 ng/ml treatments. The expression of these markers indicates that we have generated cells of the region lateral to PVN and VMH nuclei. Treatment of the EBs with FGF8 and FGF12 resulted in the expression of dynorphin and BMP7 caused the expression of MCH and NARP. Experiments are ongoing to achieve the expression of other markers like orexin and evaluate the transcriptional and physiological properties of these neuronal cells and also to obtain similar hypothalamic cells from human fibroblasts.
Conclusion: FGF and BMP signaling are involved in the expression of lateral hypothalamic marker genes.

References:
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62. Mild elevation of guanidinoacetate under partial GAMT deficiency strongly affects brain cell development

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GAMT deficiency is the most severe of creatine deficiency syndromes, characterized by creatine deficiency in CNS and guanidinoacetate accumulation. Every patient diagnosed so far was found with negligible GAMT activity (0- 4% residual activity). However, GAMT deficiency may be under-diagnosed if mutations allow sufficient residual activity to avoid creatine deficiency but enough guanidinoacetate accumulation to be toxic.
As neuropathological mechanisms are poorly known, we developed a new RNAi-induced GAMT-deficient model in 3D organotypic rat brain cell cultures by AAV2 transducing a GAMT-specific shRNA. Cultures were infected at DIV0 (AAV2/GAMT MOI: 1000), and followed during one month (harvests: DIV8, 18, 28).
RNAi led to 85% decrease of GAMT protein, which was insufficient to generate creatine deficiency. However, this partial GAMT deficiency generated a mild guanidinoacetate accumulation intracellularly (45.7 versus 4.0 nmol/mg prot) and extracellularly (9.0 versus 0.9 ?M), which led to axonal hypersprouting and decrease in natural apoptosis, followed later by induction of non-apoptotic cell death. All these guanidinoacetate-induced neuropathological effects were prevented by creatine co-treatment.
These findings show that mild guanidinoacetate accumulation without creatine deficiency is sufficient to significantly affect CNS development, and suggest that among GAMT deficiencies, more may be uncovered through guanidinoacetate increase without creatine deficiency.

63. In the pursuit of the fear engram: Identification of neuronal circuits underlying the treatment of anxiety disorder

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Fear and other anxiety disorders are extraordinarily robust and difficult to treat. Among the most efficacious treatments for anxiety disorders are exposure-based therapies, during which a patient is repeatedly confronted with the originally fear-eliciting stimulus in a safe environment so that the once fearful stimulus can be newly interpreted as neutral or safe. A fundamental element for successful
exposure-based therapies is the reactivation/recall of the traumatic memory, which initiates a time-limited process called memory reconsolidation, during which a memory becomes susceptible to disruption.
During memory reconsolidation, pharmacological means are used in order to enhance this process. Among those, histone deacetylase inhibitors (HDACis) might be a particularly promising candidate to permanently modify fearful memories for two reasons. First, by modifying chromatin compaction, epigenetic mechanisms can have potentially stable and long-lasting effects on gene expression, a required feature of long-term memories; second, epigenetic mechanisms per se can target a vast variety of nuclear processes involved in neuronal plasticity, such that their effect is not restricted to a particular signaling pathway.
Recently, it has been shown that such reconsolidation-updating mechanisms alone are not sufficient to attenuate remote (i.e. month-old) traumatic memories in mice. In particular, it was found that whereas the recall of recent memories (1d-old) induces a limited period of hippocampal neuroplasticity mediated, such plasticity was absent for remote memories. However, by using the HDAC2-targeting inhibitor (HDAC2i) CI-994 during reconsolidation, even remote memories could be persistently attenuated. Thus, applying HDACis during memory reconsolidation might constitute a treatment option for remote traumata.

64. Self-stimulation of VTA DA neurons is sufficient to mimic key features of addiction in mice

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Addictive drugs increase dopamine (DA) concentration in the ventral tegmental area (VTA) and its target areas, such as the nucleus accumbens NAc and pre-frontal cortex (PFC), which induces drug-adaptive behavior.
However, addictive drugs also have additional pharmacologic targets. Evidence that DA is sufficient to evoke the pathological synaptic and behavioral changes observed in addiction is still lacking. Here, we show that blue-light self-stimulation of VTA dopaminergic neurons infected with channel rhodopsin evoked synaptic plasticity and adaptive behavior similar to cocaine self-administration.
First, stimulation of DA neurons reinforced lever pressing and was followed by cue-induced reward seeking after a several weeks of abstinence. In parallel we observed a strengthening of excitatory synapses onto dopamine D1 receptor-expressing neurons (D1R-MSN) of the nucleus accumbens.
Moreover, when self-stimulation was associated with punishment (brief electric shock), some animals showed a strong perseverance of responding, akin to drug-consumption despite the negative consequences. Resistance to punishment for both light and cocaine were correlated with a hypoexcitability of pyramidal neurons in the prelimbic cortex. Together, these results show that self-stimulation of VTA DA neurons is sufficient to trigger key features of addiction.

65. Contrasting forms of cocaine-evoked plasticity control components of relapse

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Nucleus accumbens neurons serve to integrate information from cortical and limbic regions to direct behaviour. Addic- tive drugs are proposed to hijack this system, enabling drug-associated cues to trigger relapse to drug seeking. However, the connections affected and proof of causality remain to be established. Here we use a mouse model of delayed cue- associated cocaine seeking with ex vivo electrophysiology in optogenetically delineated circuits. We find that seeking correlates with rectifying AMPA (a-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) receptor transmission and a reduced AMPA/NMDA (N-methyl-D-aspartate) ratio at medial prefrontal cortex (mPFC) to nucleus accumbens shell D1-receptor medium-sized spiny neurons (D1R-MSNs). In contrast, the AMPA/NMDA ratio increases at ventral hippo- campus to D1R-MSNs. Optogenetic reversal of cocaine-evoked plasticity at both inputs abolishes seeking, whereas selec- tive reversal at mPFC or ventral hippocampus synapses impairs response discrimination or reduces response vigour during seeking, respectively. Taken together, we describe how information integration in the nucleus accumbens is comman- deered by cocaine at discrete synapses to allow relapse. Our approach holds promise for identifying synaptic causalities in other behavioural disorders.

66. G?o links Wingless signal transduction to Ankyrin2 to regulate the neuronal cytoskeleton

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UNIL - DPT[3], UNIL-DPT[2], UNIL - DPT[1]

Wingless (Wg) signal transduction is involved in the formation of the glutamatergic neuromuscular junction (NMJ) in Drosophila both on the pre- and postsynaptic side of the synapse. We focus our study on the presynaptic side where a non-canonical, transcription-independent Wg signaling pathway is active. We demonstrate that the alpha subunit of the heterotrimeric Go protein is expressed in the neuron and acts downstream of Wg and the receptor Frizzled2 (Fz2) in this divergent Wg-pathway. Furthermore, we show the physical and genetic interaction of G?o with the neuronal protein Ankyrin2 (Ank2). Until present, the giant isoforms of Ank2 have been thought to be static players in the synapse, binding to microtubules and linking the cytoskeleton to the plasma membrane. We identify Ank2 as a downstream target of Wg-Fz2-G?o in the synapse. The interaction of Ank2 and G?o is conserved in mammalian cells where downregulation of Ank2 shifts the formation of microtubule-dependent neurites induced by G?o to actin-based lammelipodia. Our findings describe a novel, conserved mechanism for cytoskeleton regulation in the nervous system development and function.

67. The coincident activation of lemniscal and paralemniscal inputs can drive synaptic plasticity in layer 2/3 pyramidal neurons of the mouse somatosensory cortex in vivo

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In adult animals, structural changes occur at the level of dendritic spines and axonal boutons in response to alterations in sensory experience. The causal relationship between synaptic activity and structural changes, however, is not clear. Hebbian-plasticity models predict that synapses will be stabilized at the nodes of neuronal networks that display high levels of coincident activity. Previous work from our lab shows that rhythmic (8Hz) whisker stimulation-evoked LTP (RWS-LTP) in layer (L) 2/3 pyramidal cells relies on the combined activity of lemniscal and paralemniscal pathways. Here, we targeted ChR2 expression to POm neurons using AAV-mediated gene transfer in order to optically control the activity of those inputs. As a first step, we show that photostimulation of the POm nucleus induces NMDA-dependent, sub-threshold responses in L2/3 pyramidal cells similar to those that are required for the induction of RWS-LTP. In addition, simultaneous photostimulation of POm neurons together with whisker stimulation at low frequencies (1Hz) can also elicit LTP, suggesting that coincident lemniscal and paralemniscal input can drive LTP induction. Next, we combined the ChR2-tdTomato expression in POm neurons with sparse AAV-mediated eGFP expression in L2/3 pyramidal cells in order to study the effects of coincident activity on dendritic spines. Preliminary data suggest that simultaneous photostimulation of the POm nucleus together with whisker stimulation may also affect spine dynamics. Taken together, these results indicate that the coincident activity of the convergent lemniscal and paralemniscal inputs onto L2/3 pyramidal cells may potentiate synapses and affect their stability.

68. Modulation of molecular substrates of thalamic sleep rhythms through synaptic NMDA receptors

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Thalamic circuits are reliable and stereotypic pacemakers for the generation of certain sleep rhythms. Yet, it is well known that sleep oscillations vary in intensity, due to circadian and homeostatic influences. Here, we asked: are thalamic pacemaker cells rigid elements in sleep rhythmogenesis or do they undergo activity-dependent modifications? Burst discharge in nucleus Reticularis thalami (nRt) neurons through T-type calcium channels (CaV3) is a well-described molecular mechanism underlying sleep rhythm generation, therefore, we set out to explore regulation of CaV3 signaling through glutamatergic synaptic inputs.
Mimicking elevated thalamocortical synaptic activity by enhancing ambient glutamate levels with TBOA (100µM, 3min superfusion) resulted in increased CaV3-currents in nRt cells (60±13% above baseline, n=5, $p<0.05$), as measured in patch-clamp recordings in acute slices from wild-type mice. This facilitation was mimicked by brief bath-application of NMDA (30µM, 3min)(102±22%, n=8, $p<0.01$) and largely suppressed by blockade of GluN2C-NMDARs with PPDA (500nM)(11±4%, n=7, $p>0.05$). CaV3-current increase was absent in CaV3.2-/- mice (6±5%, n=10, $p>0.05$), but not in CaV3.3-/- mice (103±16%, n=5, $p<0.01$), suggesting a glutamatergic mechanism recruiting CaV3.2 channels through activation of GluN2C-NMDARs that are expressed at both cortico-nRt and thalamo-nRt synapses. Moreover, specific photoactivation of cortical afferents (10Hz trains), induced a facilitation of CaV3-currents (38±9%, n=7, $p<0.01$), which was sensitive to PPDA (16±7%, n=6, $p>0.05$). As a result, nRt excitability was promoted, as indicated by the potentiated low-threshold spike amplitude (dV/dt increase: 32±13%, n=5) following repetitive cortical activation. These data suggest that cortical inputs trigger activity-dependent changes in the molecular cores of thalamic sleep rhythmogenesis.

69. Role of Shank3 in the postnatal development of excitatory transmission in the VTA

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Postnatal periods of development are characterized by rapid changes in neuronal networks, providing critical periods in which environmental experience can lead to long-term changes in brain and behavior. In the Ventral Tegmental Area (VTA), postnatal maturation of excitatory transmission is regulated by mGluR1, which orchestrates both the subunit composition of AMPARs and NMDARs. However, the molecular mechanisms underlying such postnatal maturation remain elusive. Shank3 is a scaffolding protein of the postsynaptic density that links group I mGluRs to NMDARs and AMPARs through its interaction with Homer proteins. To characterize the role of Shank3 in glutamatergic transmission in the VTA in vivo, we performed whole cell path clamp recordings from dopamine (DA) neurons in acute midbrain slices to record excitatory transmission. Knocking down the major isoforms of the Shank3 gene in neonatal mice disrupted the postnatal maturation of both AMPARs and NMDARs. Moreover, dissociating the Shank-Homer interaction in vitro and in vivo, we parse the relevant region, and conclude that the Proline-rich domain of Shank3 is essential for postnatal maturation. Finally, we show that only fully matured synapses are capable of expressing social experience-dependent synaptic plasticity. Mutated Shank3, implicated in autism spectrum disorders, may therefore lead to insensitivity for social experience via an incomplete postnatal maturation of excitatory transmission in the VTA.

70. Lactate neuroprotection in cerebral ischemia: what is the mechanism?

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Brain energy metabolism is a complex compartmentalized process and, besides glucose, other metabolic intermediates such as lactate, pyruvate or acetate have been shown to be oxidized for energy production. We have previously shown that L-lactate administered either after oxygen and glucose deprivation (OGD) or during reperfusion after transient middle cerebral artery occlusion (tMCAO) exerts protection against ischemic damage (Berthet et al., 2009; 2012). New evidence has risen concerning the presence and possible involvement of the Hydroxy-Carboxylic Acid Receptor-1 (HCA1) in nervous system effects of lactate (Bergersen et al., 2013; Bozzo et al., 2013). The objective of the present work was to elucidate whether the neuroprotective effects of lactate are exerted as an energy substrate or acting through the HCA1 receptor. We used OGD, tMCAO and protein expression analysis approaches to study the effects exerted by different monocarboxylates after ischemia. In vitro, the administration of D-lactate, pyruvate and the HCA-1 receptor agonist 3-5 DHBA improved cell survival 48h after OGD, while the administration of acetate and glucose did not. In vivo, the administration of D- Lactate reduced lesion size and improved the neurological performance. We observed an increase in HCA1 protein expression in the hippocampal slices subjected to OGD and in the primary cortex surrounding the lesion site, 24h after tMCAO. When L-lactate was administered intravenously at reperfusion, there was a further HCA1 increase in the lesion site. We believe lactate exerts its effects using both mechanisms, by being metabolized and by acting as a signaling molecule through the HCA1 receptor.

71. Involvement of the receptor for advanced glycation end-product (RAGE) in redox dysregulation and neuroinflammation in an animal model of schizophrenia.

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Schizophrenia is a major psychiatric disease which involves both genetic and environmental factors. Glutathione (GSH), an important cellular antioxidant and redox regulator, is decreased in CSF and brain of patients. The key GSH synthesizing genes present polymorphisms associated with the disease. Thus, redox dysregulation during neurodevelopment is a critical risk factor for schizophrenia, on which converge genetic impairments of glutathione synthesis and environmental factors generating oxidative stress. Increasing evidence also points to immune dysregulation in schizophrenia, highlighted by anomalies of immune-related genes in brain. However, the causes and underlying mechanisms of this inflammatory-like state are still unclear. As oxidative stress is known to induce inflammatory processes, the latter were studied in a transgenic animal model with GSH deficit (GCLM-/-). RAGE represents one potential link between these two processes, as it is activated by ROS and induces inflammatory gene. We studied microglia activation and pathways involving RAGE in the anterior cingulate cortex in GCLM-/- and WT mice at P40 following oxidative stress induction by a dopamine uptake blocker between P30 and P40. The number of Iba1-immunoreactive (IR), CD11b-IR and CD68-IR cells were increased in GCLM-/- compared to WT at basal level, suggesting a pro-inflammatory state. RAGE cleavage was increased in the GCLM-/- at basal level but decreased after oxidative stress induction. In addition, S100b, a ligand of RAGE, and MMP9, a metalloproteinase potentially involved in RAGE cleavage, were also increased in the GCLM-/- at basal level. These inflammatory process anomalies occurring during brain development may induce structural impairments related to schizophrenia.

72. Subunit interactions control ASIC activity

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Acid-sensing ion channels (ASICs) are voltage-independent, proton-activated channels. They are implicated in the expression of fear, pain perception and diseases associated with a tissue acidification. ASIC subunits are composed of two transmembrane domains, intracellular N- and C-termini and a large ectodomain with the sub-domains palm, thumb, finger, knuckle and ?-ball. Three subunits are required to form a functional channel and interactions between subunits are important for the assembly and stability of the channel. We investigated here the role of intersubunit interactions for ASIC function. We show that formation of an engineered disulfide bond between the palm and thumb domains leads to partial channel closing. Disulfide bonds between Glu235 of the finger loop and two different residues of the knuckle did either open or close the channel. Voltage-clamp fluorometry experiments showed that both the finger loop and the knuckle move during acidification and subsequent desensitization away from Trp233 of the B-ball. This study shows that intersubunit interactions are critical for ASIC function and indicates that the interaction surface between subunits changes during ASIC activity.

73. Genome editing with viral-delivered CRISPR/Cas9 system for Huntington's disease

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Huntington's disease 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. A promising approach consists to directly repair the mutant HTT gene using targeted site-specific nucleases. The recently described Clustered Regularly Interspaced Short Palindromic Repeats system (CRISPR) offers the possibility to direct a bacterial nuclease, Cas9, using small guide RNA sequences (sgRNA) to a specific DNA target site. In this study, we propose to characterize and optimize the CRISPR/Cas9 system for in vitro and in vivo DNA repair, with an application for Huntington's disease.

As a proof-of-principle of gene editing with this technology, we targeted an artificial sequence containing fluorescent reporter genes to facilitate the readout in HEK 293T cells. We were able to reach up to 45% of DSB formation both in transient transfection and with lentiviral vectors. Co-delivery of the CRISPR system and a DNA template carrying homology for the target site provides more than 25% of HR in our cells. Green fluorescence protein targeting both in rodent primary neuronal cultures or in the adult mouse brain (BAC Drd1/Drd2-eGFP transgenic mice) was efficiently performed using the CRISPR system. We are currently using this approach to evaluate strategies for mutant HTT repair in HD rodent and human cells.

74. Cell-type specific expression of mutant huntingtin in the mouse striatum with AAV2/5 viral vectors

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Huntington's disease (HD) is a rare neurodegenerative disease caused by an autosomal dominant mutation on the gene coding for the huntingtin protein (HTT). Despite ubiquitous expression of the mutant HTT, a selective vulnerability of medium spiny neurons (MSNs) of the striatum is observed at the early stages of the disease. However, recent data have suggested the implication of non-neuronal cells in the disease, in particular astrocytes, and an increasing number of studies have demonstrated the essential role of glial cells in many neuronal functions. These underline the need to better characterize neuron-astrocyte interactions specifically in HD.
In this study, we propose to characterize a viral HD model using an AAV2/5 expressing a short mutant HTT fragment under the control of either a neuronal or an astrocytic promoter. We first observed that the combination of AAV2/5 and the chicken ? actin (CBA) promoter offered the possibility to express in vivo a reporter gene specifically in neurons with a high expression rate. Replacement of this reporter gene by mutant HTT led to a neuron-specific formation of aggregates from 4 weeks to 12 weeks post-infection. Furthermore we characterized several molecular and behavioral hallmarks relevant to HD and their evolution in this model. We are currently optimizing the AAV2/5 with astrocytic promoters for astrocyte-specific expression of mutant HTT, which will allow us to make a direct comparison between neuron and glial-specific models in order to better understand neurons-astrocytes interactions in HD.

75. A subset of VTA neurons provides both inhibitory and excitatory transmission to the hippocampus.

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The ventral tegmental area (VTA) is a component of the mesolimbic reward circuit essential for learning the association between predicting stimuli and motivationally-relevant outcomes. While dopaminergic cells, the principal VTA neuronal population, attracted most of the interest for this structure, not as much attention has been focused on the less represented GABAergic or glutamatergic populations.
We report here the identification of a peculiar VTA neuronal population that sends long-range projections to innervate the hippocampus in the mouse.
Using GAD65-Cre mice, retrograde tracing and optogenetic tools combined with in vitro electrophysiological recordings of acute VTA and hippocampal brain slices, we show that VTA GABAergic neurons make functional synapses in the granule cell layer of the dentate gyrus (DG) and, to a lesser extent, in the strata radiatum, pyramidale and oriens of the CA2 region. In vitro optical stimulation of these ChR2-expressing terminals during voltage clamp recordings gives rise to small postsynaptic currents (PSCs) onto DG granule cells. Surprisingly, pharmacological antagonism or blockade of the ionotropic GABAA receptor with bicuculline or picrotoxin, is not able to completely abolish light-evoked PSCs, revealing a residual current that is sensitive to the AMPA/kainate receptor antagonist NBQX. Similarly, using VGLUT2-Cre mice we show the presence of glutamate-releasing neurons in the VTA that project onto DG granule cells, where they elicit bicuculline- and NBQX- sensitive PSCs.
Altogether, the present data hints at the existence of a previously undescribed population of VTA neurons with mixed GABAergic/glutamatergic phenotype that provides a direct connection to the DG.

76. PAG Glutamate neurons encode the aversive component of pain.

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The Periaqueductal Gray (PAG) has been identified as a main descending pain modulator and it is also involved in defensive behaviors. While most of previous studies have focused on the analgesic properties of the PAG, the acute response to noxious stimuli and the related circuitry involved is yet unexplored.
First, in vivo recordings in isoflurane-anesthetized mice revealed a strong excitation of optogenetically identified Glutamate PAG neurons, in response to a foot shock. Then the use of a cre-dependent anterograde transsynaptic tracer revealed the connectivity between these PAG Glutamate neurons and GABAergic neurons of the ventral tegmental area (VTA). In addition, in vitro electrophysiological recordings of VTA GABAergic cells confirmed the functional nature of this pathway. Finally at the behavioral level, optogenetic activation of these terminals induced place avoidance in freely moving mice.
VTA GABAergic neurons are known to inhibit dopaminergic cell activity and have been shown to be excited following a foot shock. This new evidence provides insight into the excitatory inputs to these neurons when a painful stimulus is presented.
The aversive nature of the PAG-Glutamate neurons to VTA GABAergic cells pathway, in conjunction with the acute response to a foot shock, suggests that in addition to pain modulation through endogenous opioid signaling, the PAG conveys a crucial message to the brain, where the aversive and potentially dangerous characteristic of a noxious stimulus is encoded through the modulation of the reward system via the VTA.

Neurological or Psychiatric Conditions

77. Age-related reduction of the default mode network structural connectivity in 22q11.2 deletion syndrome

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Neural endophenotype associated with 22q11.2 deletion syndrome (22q11DS) includes brain structural alterations and deviant developmental trajectories. Resting state fMRI findings reported functional dysconnectivity within the Default Mode Network (DMN). We explored the relationship between functional and structural DMN connectivity and their development with age in patients with 22q11DS compared with controls. Given the role of the DMN in sustaining metacognition, we further aimed to investigate the relationship between DMN connectivity and the manifestation of maladaptive metacognitive beliefs.

Structural and resting-state functional MRIs were acquired from 41 patients with 22q11DS and 43 controls (age 6-28 years old). The DMN was identified through Independent Component Analysis and Regions of Interest were defined for the functional/structural connectivity measures. Metacognitive beliefs were assessed in adolescents and adults using the Metacognitive Questionnaire (MCQ). Connectivity measures were compared between groups in the whole population of 22q11DS and controls as well as in three different age bins, and correlated with the MCQ scores.

We observed a simultaneous reduction of functional and structural connectivity in the anterior-posterior DMN network. In particular, structural connectivity measures were mainly affected in adults with 22q11DS. Furthermore, the decrease in structural connectivity correlated with the manifestation of maladaptive metacognitive beliefs.

In 22q11DS, dysconnectivity can be observed within the DMN for functional and structural connections. Furthermore, patients with 22q11DS fail to normally develop structural connections between some DMN networks. Finally, metacognitive impairments appear to be sustained by reduced structural connectivity in the DMN, informing a possible conceptualization of emerging psychosis.

78. Modelling redox dysregulation in schizophrenia: deficient glutathione synthesis impairs white matter structure and function in the mouse

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Background: Oxidative stress and redox dysregulation are involved in schizophrenia pathogenesis. However, it is unknown if they are releted to the white matter anomalies often observed in patients.
Method: We used a mouse model (Gclm KO) with weakened synthesis of the antioxidant and redox regulator glutathione due to deletion of the modulator subunit of the glutamate-cysteine ligase, the rate-limiting enzyme for glutathione synthesis. We explored white matter (WM) integrity along postnatal development in the brain of KO and wild-type (WT) mice using diffusion tensor imaging. Significant differences were further investigated in by immunohistochemistry of myelin-associated proteins and in vitro electrophysiology. We also assessed ventricular volume in T2-weighted images and the neurochemical profile of the prefrontal cortex with magnetic resonance spectroscopy.
Results: Reduced fractional anisotropy in the anterior commissure (AC, -7.5%±1.9, $p<0.01$) and fornix-fimbria (FF, -4.5%±1.3, $p<0.05$) in KO mice were accompanied by reduced conduction velocity in the fast-conducting fibers of the posterior limb of the AC (-14.3%, $p<0.05$), the slow-conducting fibers of the FF (-8.7%, $p<0.05$), reduction of myelin basic protein immunoreactivity in the AC (-18.8%±9.2, $p<0.05$) and ventricular enlargement at juvenile age (+25.0%±8.1 $p<0.05$).
Conclusions: A genetic deficit in glutathione synthesis affects WM integrity and conduction velocity in specific tracts. This suggests that redox dysregulation contributes to compromised WM structure/function together with ventricular enlargement, the two most frequent anatomical phenotypes in the brain of schizophrenia patients.

79. Leptin receptor signaling is impaired in compulsive overeating rats

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Background: Compulsive overeating is a loss of control over food intake most likely reflecting disturbances in the rewarding system. Compulsive overeating is often accompanied by metabolic alterations and psychiatric disorders. Recent evidence suggests that extra-hypothalamic activity of leptin signaling is implicated both in food motivation and mood regulation. The present study investigated whether rats exposed to intermittent access to palatable food, developed changes in brain-expression of LepRb and other genes involved in the regulation of food intake, mood and stress (Crtc1, Bdnf and Crf1).?

Methods: Wistar-Hann rats were assigned to a control group receiving standard chow along all the procedure (C/C group) or to an experimental group receiving alternate access to a palatable food, two consecutive days per week (C/P group). Once the feeding protocol finished, compulsive overeating was assessed using an operant-conditioning procedure and gene expression was measured by RT-PCR.?

Results: In contrast to controls, C/P rats showed, binge eating behavior and compulsivity for palatable food (two-way ANOVA: group=$F[1,50]=19.562$, $p<0.0001$). Post-mortem analysis demonstrated a significant rise of LepRb in the hippocampus (C/C=1.059, C/P=1.523, $p<0.05$) and a reduction in the amygdala (C/C =1.131, C/P=0.586, $p<0.05$) and prefrontal cortex (PFC) (C/C=1.038, C/P=0.641, $p<0.05$). Reduced Crtc1 and Bdnf expression levels were also observed in the PFC and amydala, respectively.?

Conclusions: Our findings suggest that compulsive overeating may be related to alterations in leptin signaling and support the possibility that impairment in the extra-hypothalamic activity of this adipokine may affect motivation for food reward and contribute to the onset of anxiety and depressive-like behaviors.?

80. Lagged synchronization of source EEG shows functional disconnection in patients with psychogenic non-epileptic seizures

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CHUV[1], CHUv[2]

Psychogenic nonepileptic seizures (PNES) are involuntary paroxysmal events, which are unaccompanied by epileptiform EEG discharges. We hypothesized that PNES are a disorder of distributed brain networks resulting from their functional disconnection. The disconnection may underlie a dissociation mechanism that weakens the influence of unconsciously presented traumatizing information but exerts maladaptive effects leading to episodic failures of behavioral control manifested by psychogenic "seizures". To test this hypothesis, we compared functional connectivity (FC) derived from resting state high-density EEGs of 18 PNES patients and 18 age- and gender-matched controls. To this end, the EEGs were transformed into source space using the LAURA inverse solution. FC was estimated with a multivariate measure of lagged dependency in the theta, alpha, and beta frequency bands for 66 brain sites clustered into 18 regions. SubNetwork Based Analysis was applied to extract significant between-group differences in inter- and intraregional FC. The significant effect of PNES – a decrease in lagged FC between the basal ganglia (BG) and limbic, prefrontal, temporal, parietal, and occipital regions – was found in the alpha band. These findings reveal a possible neurobiological substrate of PNES, which explains both attenuation of the effect of potentially disturbing mental representations and the occurrence of PNES episodes. By improving our understanding of the etiology of this condition, our results potentially lead to a refinement of diagnostic criteria and management principles.

81. Involvement of the agmatinergic system in the depressive-like phenotype of CRTC1-deficient mice

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SUPEA/CHUV[2], CNP/CHUV[1]

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 the agmatinergic system is impaired in mood disorders patients. Our group has generated a CRTC1-deficient mouse line which presents an important behavioural and molecular depressive-like phenotype, as well as blunted response to classical antidepressants. Unpublished microarray data from our group showed an increased expression of agmatinase (the agmatine-degrading enzyme) in the cortex of Crtc1-/- mice, suggesting that the agmatinergic system of these mice might be impaired. We were therefore interested in investigating the link between this system and the CREB-CRTC1 pathway.

We first confirmed the increased agmatinase expression displayed by the Crtc1-/-mice at the mRNA and protein levels and indeed found that it was overexpressed in the hippocampus and prefrontal cortex of these animals. Preliminary immunohistochemical data suggest that Crtc1-/- mice display more agmatinase-expressing cells than wild-type mice, mostly interneurons, in several brain regions, including the prefrontal cortex and the CA1 region of the hippocampus. At the behavioural level, we found that acute agmatine treatment was able to reduce the increased immobility time displayed by Crtc1-/- mice in the Forced-Swim Test. Molecular effects of agmatine on wild-type and Crtc1-/- mice are currently being investigated.

Altogether, these data support the involvement of the agmatinergic system in the depressive-like phenotype of Crtc1-/- mice, and also allow a better understanding of the agmatinergic system and its putative role in major depression.

82. Generative theoretical framework linking brain anatomy and clinical phenotype in mood disorders

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CHUV[1]

Aim and background: Mood disorders' (MD) current diagnostic criteria are not strictly based on objective measures of behaviour and fail to provide an accurate and robust diagnosis and prognosis of clinical outcome. We aimed at providing a composite biomarker integrating clinical information along the cognitive-anxiety-personality-emotions (CAPE) axis with brain anatomy.
Methods: We acquired clinical and CAPE data in patients with bipolar disorder (BD), major depressive disorder (MDD) patients, age-gender matched healthy controls and their offspring. Quantitative MRI provided estimates of grey matter volume and brain tissue properties - myelin, iron and water. Individuals' CAPE was correlated to brain anatomy and validated for diagnostic accuracy across probands. The model was then applied to the offspring, tested against their parents' and own diagnosis.
Results: Results indicated that the CAPE profile differentiates MD patients from controls, but not between BD and MDD. CAPE model classified correctly the offspring cohort according to their own clinical diagnosis, but not to their parent diagnosis. We report a strong correlation between CAPE and complex pattern of brain anatomy changes including key regions of limbic and associative circuits.
Conclusion: We show distinct patterns of brain tissue property and grey matter volume changes linking CAPE features allowing for accurate prediction of clinical phenotype in MD patients. The proposed composite biomarker proves useful in the reliable description of MD patients and their offspring. The concept of a composite biomarker is readily applicable for the study of complex behavioural patterns and their impact on brain anatomy in mental diseases.

83. Metabolic deterioration and altered brain morphology in insulin resistance: linking diabetic encephalopathy and Alzheimer's disease

Duarte J.

EPFL - Other

Insulin signalling is involved in metabolic regulation and synaptic plasticity, thus controlling brain function. Deterioration of brain insulin signalling occurs in Alzheimer's disease (AD) and diabetes. Non-obese insulin-resistant Goto-Kakizaki (GK) rats display synaptic degeneration, astrogliosis and memory impairment, which are features of dementia and early stages of AD. Using high-field (14.1 T) magnetic resonance imaging (MRI) and spectroscopy (MRS) we now found that GK rats display altered brain morphology, namely reduced volume of the cerebrum ($P<0.001$), cortex ($P<0.001$) and hippocampus ($P<0.001$), and increased volume of ventricles ($P<0.001$), compared to Wistar rats. Furthermore, altered neurochemical profiles in the cortex and hippocampus are patent in GK rats. Most importantly, the concentrations of glutamine ($r=0.59$, $P<0.001$), alanine ($r=0.38$, $P=0.043$), taurine ($r=-0.51$, $P<0.001$), phosphorylethanolamine ($r=0.57$, $P<0.001$), ascorbate ($r=-0.50$, $P<0.001$), N-acetylaspartylglutamate ($r=0.41$, $P=0.005$) and choline ($r=0.42$, $P=0.001$) in the hippocampus, were associated with performance in a Y-maze spatial memory test. This study provides biomarkers of structural deterioration and brain function that can be monitored non-invasively and pave the way for clinical applications, diagnosis and therapy monitoring.

84. Investigating the mechanisms of generation of epileptic networks in a mouse model of temporal lobe epilepsy

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Epilepsy is one of the most frequent neurological disorders and is typically divided into focal and primary generalized types. In focal epilepsies, a localized brain area, also named seizure-onset zone, accounts for the generation of ictal and possibly interictal events. Yet, strong evidences suggest that even the development of focal epileptic activity is dependent on the establishment of an epileptic network that involves areas remote from the localized focus. Moreover, it is highly suspected that the epileptic focus is not independent within brain networks, ie. the focus affects large-scale brain networks and modify their activity even if they are not disturbed by the initial injury.
Here, we study the development of epileptic nertworks in a model of hippocampal sclerosis in awake mice that were previously injected unilaterally in the hippocampus with kainate. We record the brain activity using 32 electrodes distributed equally over both hemispheres. Baseline EEG were recorded before the kainate injection, allowing us to identify the background activity and typical graphoelements. These components of the spontaneous “pre-injected” brain were compared to post-injection spontaneous brain activity. We present here evidence that the focal induction of an epileptic disease has widespread consequences.

85. EEG time-varying effective connectivity in left and right temporal lobe epilepsy

Coito A.

UNIGE - HUG

We aimed to analyze the dynamic behavior of epileptic networks through the study of the effective connectivity at a whole-brain scale during interictal spikes in left and right temporal lobe epilepsy (LTLE and RTLE) using high-resolution EEG signals.
Sixteen patients, 8 with RTLE and 8 with LTLE, were selected for the study. We assessed the connectivity changes of cortical networks during interictal spikes compared to baseline periods (no pathological activity) at high temporal resolution, using high density EEG recordings. The electric source activity was obtained for 82 cortical regions of interest (ROI) using an individual head model and a distributed linear inverse solution. A multivariate, time-varying Granger causal modeling method was applied to the source signal of all ROIs. A non-parametric statistical test was carried out to assess the difference in outflow, in each ROI, between interictal spikes vs baseline epochs.
The key driving structures were located in the medial temporal pole for both groups. A different driving pattern between LTLE and RTLE was found. In LTLE the keys drivers were on the ipsilateral side while in RTLE the key drivers were in both ipsilateral and contralateral areas. Moreover, in RTLE we observed a transcallosal driving pattern (from the ipsilateral to the contralateral regions) that was not seen in LTLE. The localization of the main drivers, for all the patients, was concordant with the epileptogenic zone estimated invasively.
This enhanced characterization of the epileptic networks contributes for the understanding of these conditions and could have clinical implications for epilepsy surgery.

Neuron-glia interactions

86. Structural analysis of the neurogenic niche in the adult hippocampus

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Adult mammalian hippocampal neurogenesis consists in the generation of new neurons from neural precursors located in the subgranular zone of the dentate gyrus.

Learning experiences and neuronal activity increase adult neurogenesis and increasing or reducing neurogenesis leads to corresponding changes in memory performances, suggesting a role of these cells in learning and memory. Hippocampal 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 interaction between these cells and the adult neural stem cell, Radial Glia Like cell (RGL) is crucial for a full understanding of the function of the neurogenic niche.

Here, we are using morphological approaches to identify RGL, niche cells and the nature of their interactions. We have started testing whether these interactions change in conditions with enhanced (voluntary running) or reduced (aging) neurogenesis.

87. The implication of miRNAs in regulating basal MCT2 expression by cultured cortical neurons

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UNIL - DP

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 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-132 and miR-134. Then, we confirmed the presence of those miRs in primary cultures of mouse cortical neurons with qPCR. Finally, to determine if miR-132 and miR-134 were regulating MCT2 expression, we transfected cultured cortical neurons with the corresponding anti-miRs. Our preliminary results revealed an increase of MCT2 protein expression after anti-miR-134 treatment but not after anti-miR-132 treatment. These data suggest that miR-134 is implicated in the regulation of basal MCT2 expression by cultured cortical neurons.
This work was supported by Swiss Fonds National de la Recherche grant n° 3100A3_140957 to LP.

88. Disrupting astrocyte-neuron lactate transport persistently reduces cocaine-seeking behaviour

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A central problem in the treatment of drug addiction is the high risk of relapse often precipitated by drug-associated cues. Although memories have been shown to become labile soon after reactivation of mnemonic traces during a memory reconsolidation process that depends on protein synthesis, the role of astrocyte-neuron lactate transport in long-term conditioning has received little attention. By infusing an inhibitor of glycogen phosphorylase, 1,4-dideoxy-1,4-imino-D-arabinitol (DAB, 300pmol), into the basolateral amygdala of rats, we report that disruption of astrocyte-derived lactate not only transiently impairs the acquisition of a cocaine-induced conditioned place preference, but also can persistently disrupt an established conditioning. We also demonstrate that the preference for the cocaine-paired compartment is rescued by L-Lactate co-administration whereas co-administration of DAB and Pyruvate failed to do so. In contrast, rats injected with DAB in home cages 24h prior the test exhibited a strong CPP, suggesting a role of DAB on experience-dependent memory reconsolidation. Molecular studies suggested a mechanism requiring the synaptic plasticity related transcription factor Zif268 but not the brain-derived neurotrophic factor (BDNF). In complement, we show that the long-term amnesia induced by glycogenolyis inhibition and the concomitant decreased expression of the extracellular signal-regulated kinase (ERK) protein are both restored with L-Lactate co-administration. Our results reveal a signalling role of astrocyte-derived lactate in positive memory formation and highlight a novel amygdala-dependent reconsolidation process that can be disrupted to reduce the long-lasting impact of drug cues on drug seeking.

89. Increased neuronal oxidative metabolism during focal cortical activity compared to resting

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EPFL[1], EPFL, UNIGE, UNIL[2]

Brain energy metabolism is compartmentalized between neurons and astrocytes. Although both cell types exert control over synaptic transmission, the relevance of astrocytic metabolic pathways coupled to brain activity is matter of debate. The compartmentation of energy metabolism underlying brain activity can be studied in vivo by 13C magnetic resonance spectroscopy (MRS) during sustained and prolonged somatosensory stimulation. High resolution 13C MRS was performed at 14.1 T in the rat cortex (93.5 ?L voxel) during [1,6-13C]glucose infusion under ?-chloralose anesthesia. Electrical stimulation was performed with stainless steel electrodes inserted into both forepaws and hindpaws following the paradigm [30 sec ON – 10 sec OFF] at variable frequency (2-3 Hz) repeated for four hours. Cortical activation was confirmed by blood oxygenation level-dependent functional magnetic resonance imaging using gradient echo echo planar imaging (GE-EPI). 1H and 13C MRS were performed with STEAM and semi-adiabatic distortionless enhancement by polarization transfer (DEPT), respectively, and spectra were analyzed with LCModel. 13C enrichment curves of aliphatic carbons of glutamate, glutamine and aspartate were quantified and analyzed with a mathematical model of brain energy metabolism. Preliminary results from rats under stimulated brain activity (n=7) and resting (n=8) indicate that the neuron-glia interactions adapt to different brain activity states in such a way that focal cortical activity likely increases neuronal oxidative metabolism, supporting increased neurotransmission rates.

Sensory and Motor Systems

90. Neuroprosthetic rehabilitation restores supraspinal control of movement after a severe acute and chronic contusion of the spinal cord

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EPFL - BMI[1]

Neuroprosthetic rehabilitation combining electrochemical neuromodulation of spinal circuits and robot-assisted training re-established supraspinal control of locomotion after staggered spinal cord hemisections. Here, we evaluated the capacity of this intervention to improve motor control after a more clinically relevant spinal cord injury (SCI), both acute and chronic. Adult rats received a severe mid-thoracic contusion that spared less than 10% of descending fibers and led to permanent paralysis. After two months of training, all the rats were able to walk overground and climb staircases while supporting their entire body weight under electrochemical stimulations. Moreover, approximately half of the trained animals displayed weight-bearing leg movements, and were capable of swimming continuously in the complete absence of enabling factors. In contrast, none of the non-trained rats recovered any spontaneous hindlimb locomotion. After two months of training, rats with chronic contusion SCI regained the ability to initiate and sustain overground locomotion and climb staircases, but only in the presence of electrochemical neuromodulation. Moreover, they showed limited weight-bearing capacities and more pronounced gait impairments compared to rats trained in the sub-acute phase of SCI. Our results confirm the ability of neuroprosthetic rehabilitation to re-establish supraspinal control of leg movement after a severe SCI, and expand its therapeutic potential to more clinically relevant lesions, settings, and outcomes. These findings also illustrate the limitation of this intervention, providing useful framework to translate neuroprosthetic rehabilitation into medical practices to improve motor recovery after spinal cord injury.

91. Neuroanatomical correlates of perceptual learning in the mouse neocortex

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We are interested in the structural mechanisms and strategies that cortical neurons use to change circuit function during perceptual learning. Recent studies have indicated that the activity of only a few sensory neurons is enough to mediate perception and behavior. This suggests that alterations in the synaptic connectivity of a few neurons could drive perceptual learning and behavior. In some learning tasks, the extent of structural synaptic plasticity was shown to correlate with the improvement in behavioral performance. However, these studies did not unequivocally demonstrate that the neurons displaying the changes were causally related to the improvement of behavior. In order to probe structural changes in neurons that are necessary for a perceptual task we train adult mice to report the optical microstimulation of a few hundred somatosensory L2/3 pyramidal neurons expressing channelrhodopsin (ChR2). Only the axons of the microstimulated neurons can provide the information required for this perceptual task. We hypothesize that structural changes of those axons will favor the downstream signalling needed for the behavioral performance. Using 2-photon laser scanning microscopy, we repeatedly image and reconstruct large volumes of supragranular layers during the learning period in order to capture axonal structures of a subset of the ChR2-expressing neurons. We have begun to employ automated segmentation algorithms to analyze synaptic structural changes. We will show the behavioral data and preliminary structural analyses.

92. A novel behavioral paradigm for goal directed reaching in head-fixed mice

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Reaching out to manipulate objects is fundamental to most of what we do, yet the neuronal circuits underlying these movements remain poorly understood. Although studies in primates and rats suggest that frontal cortex plays a fundamental role in different aspects of these movements, the organizational details remain controversial.
To further dissect the neuronal dynamics involved in goal directed action a wide range of molecular, optogenetic and optical imaging tools would be necessary. These tools are readily available for mice, but the related behavioral paradigms for head-fixed mice do not yet exist.
Inspired by classic reaching tasks in primates, we have developed a novel behavioral paradigm to study goal directed reaching in mice. Head-fixed mice were trained to use their forepaw to reach out and grab sweet rewards presented at different target locations. After 2 weeks of training the mice were able to accurately locate the rewards and perform hundreds of successful reaches per session. An automated behavioral control system allowed us to follow several behavioral features in real time.
To causally dissect the cortical areas involved in this task, we optogenetically silenced different frontal cortex locations. Our results show that motor cortex inactivation significantly affects goal directed reaches. Inactivation of contralateral motor cortex, for example, almost completely halted the initiation of reaching movement.
These preliminary experiments illustrate that head-fixed mice can be trained on complex motor tasks. Moreover, we confirmed that, as in primates, motor cortex plays a key role in executing goal directed reaching movement in mice.

93. Uncovering and enhancing motor cortex contribution to locomotor recovery after spinal cord injury in mice

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We previously demonstrated that robot-assisted training enabled by an electrochemical spinal neuroprosthesis restored supraspinal control of locomotion in rats with a spinal cord injury (SCI) leading to permanent paralysis. Training encouraged the motor cortex to elaborate alternative relay pathways that restored versatile access to electrochemically-enabled lumbosacral circuits. However, the mechanisms through which the motor cortex engages and modulates electrochemically-enabled spinal circuits remain unknown. To address this question, we established a research platform in mice through which neural activity can be selectively manipulated under controlled conditions. We chronically implanted an optic fiber over this specific region of interest. Mice received a contusion SCI that completely interrupted the corticospinal tract, and led to severe hindlimb impairments. Functional recovery was evaluated using a high-fidelity robotic interface that provided bodyweight support against gravity, and adjustable horizontal force to facilitate walking in the forward direction. Photoactivation of the motor cortex during chemically enabled motor states instantly triggered continuous, weight-bearing locomotion in mice that failed to initiate walking. The degree of limb extension and overall locomotor output directly correlated with the intensity of photoactivation. These findings show that the motor cortex retains a remarkable degree of control over spinal locomotor circuits following a severe spinal cord injury that abolishes direct corticospinal inputs and only spares 10% of original descending pathways. However, these capabilities only manifest during chemically enabled motor states and are not accessed naturally without training. These preliminary results establish the settings to dissect and enhance the contribution of descending pathways to recovery after SCI.

94. Characterization of superficial cortical inhibitory neurons in vivo

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BioEM - EPFL[2], UNIGE - CMU[1]

The somatosensory cortex is comprised of a vast network of excitatory and inhibitory neurons. Inhibitory neurons strongly shape the processing of sensory input, and provide a powerful source for regulating cortical plasticity. Inhibition is governed by a diverse group of interneurons, which not only synapse on excitatory neurons but also onto one another. Depending on subtype, inhibitory interneurons specifically target different cortical layers, subtypes of excitatory or inhibitory neurons or even segments of neurons (e.g. dendrites, somas or axons; dendritic spines or dendritic shafts). We have started studies aiming at the characterization of the activity, synaptic connectivity and morphological plasticity of parvalbumin (PV) and vasoactive intestinal peptide (VIP) expressing interneurons that are located in L1 and L2 of the mouse somatosensory cortex. We combine targeted injections of AAVFlexGFP or AAVFlexGCaMP5/6 in the barrel cortex of transgenic mice expressing Cre recombinase in PV and VIP cells. In ongoing experiments we use longterm n vivo imaging by 2photon laser scanning microscopy (2PLSM) through a glass cranial window that is implanted above the barrel cortex to characterize Ca2+ activity in cell bodies and neuropil, as well as the dynamics of axonal boutons and dendritic spines in vivo. We have collected material for focused ion beam scanning electron microscopy (FIBSEM) and the serial sections based reconstruction of imaged axon segments in order to characterize the location and ultrastructure of their synapses. As yet we have reconstructed one axonal segment of a PVcell, which indicates that synapses are formed on spineous, presumably pyramidal cell dendrites.

95. Biomarkers of visual and kinesthetic bodily representations : an fMRI study.

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How is the body represented in the brain? By answering this question several sensorimotor disorders could ultimately be better comprehended and alleviated. Previous work suggested that mental processing of bodily images can offer a window onto the nature of bodily representations. For example, mental rotation of hands, but not full-bodies, is sensitive to postural changes, suggesting that the former is based on kinesthetic information while the latter recruits visual mechanisms [Ionta et al., 2012]. If this is true, different patterns of brain activity can be hypothesized relatively to these two tasks. Namely, hand rotation should predominantly display enhanced activity in the sensorimotor network, while full-body rotation should mainly activate the higher visual cortex.
To investigate this hypothesis, we recorded fMRI data from 16 young adults performing a laterality judgment of pictures of hands and full-bodies. Our results showed that full-body laterality judgment was associated with significantly ($P<0.001$) increased bilateral activity in a broad region around the extrastriate body area (EBA), while hand laterality judgment enhanced activity in pre-SMA. This provides an important piece of evidence supporting that hands and full-bodies mental processing involves different neural systems, with the former recruiting mainly kinesthetic representations, while the later predominantly relies on the visual representations. This is consistent with the view of mental hand rotation interacting with the body schema, integrating multimodal information as touch and proprioception, while full-body rotation relies on a more pictorial and visual representation as the body image.

96. Scale-free dynamics during listening: a signature for impairment?

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Self-organized criticality and scale-free, multifractal processes have raised great, perhaps excessive, interest in recent years, both for their potentially appealing clinical applications and their mathematically solid, albeit rather new, methodological support. However, evidence for criticality remained, in our opinion, fundamentally scarce, because of narrow frequency ranges (often limited to two decades) and poor fitting methods, resulting in a bias towards power-law distributions. Even more important is the fundamental issue of interpreting criticality from the functional perspective: what does criticality mean for the brain? A physical system poised at criticality does not possess any peculiar temporal or spatial scale (it is indeed a scale-free system), and its correlations length sharply diverges. Why would a healthy brain, then, be closer to criticality than a damaged one, as suggested in many recent articles? We argue against this hypothesis, using three datasets coming respectively from Dyslexic, Autist and Control group, whose brain electrical activity (EEG) was recorded inside a functional Magnetic Resonance Imaging (fMRI) scanner, while subjects were listening to various sounds. We look both at the frequency spectra of these three groups and at the distribution in time of brain microstates, by applying proper multifractal wavelet analysis to derive the Hurst exponent for each subject and group. In addition, we aim to correlate the distribution of hurst exponents across groups with the prevalence of the Default Mode Network observed with fMRI.

Signalling and Excitability

97. 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 can subsequently elicit fear-related responses by itself. While plasticity of converging signals onto a single lateral amygdala (LA) neuron has been extensively studied to underlie this process, little is known about the role of LA sub-networks in fear-memory encoding.

We hypothesize that fear signals are re-integrated in the LA through local neuronal assemblies. To study these, we used whole-cell patch-clamp recordings to simultaneously access up to 12 neurons in acute horizontal rat brain slices, with the aim of mapping network topology and enhancing our understanding of transmission and plasticity of LA-to-LA synapses.

We observed an absence of hub neurons and an overall direct connectivity of 2%, with the chance to observe a connection decreasing with inter-somatic distance. Together, these findings suggest that LA neurons are organized into a small-world rather than a scale-free network.

Plasticity was assessed by pairing 15 pre- and post- synaptic trains at 30 Hz, with a 10ms delay between pre- and post- synaptic stimulation. This led to a potentiated redistribution of the amplitude of EPSPs, which was transient unless 1 mM Glutamine, a Glutamate precursor, was co-incubated.

Since directions of LA-LA connections seemed to be random, we monitored the propagating pathway of a spontaneously-generated brust signal, in the LA. The burst spread from caudal to medial to rostral LA with a delay of 68±31ms between caudal and rostral ends.

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Techniques in Neuroscience

98. Antidepressant-like behavioral effects of lactate

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Increasing evidence indicates that physical exercise produces antidepressant effects and complements antidepressant medications and psychotherapy. During exercise, blood lactate concentration increases and lactate is transported down its concentration gradient into the brain. Recent data have shown that lactate upregulates the expression of synaptic plasticity-related genes including BDNF (Yang J et al, PNAS in press). With regard to the role of BDNF, substantial evidence supports the involvement of BDNF in the pathophysiology and treatment of depression. In particular, the reduction of depressive symptoms by exercise is accompanied by increased levels of hippocampal BDNF and is abolished in BDNF-deficient mice. Together, these observations led us to hypothesize that regulation of BDNF by lactate in the hippocampus may contribute to the antidepressant effects of exercise.
As a proof of concept, we first examined whether intravenous injection of lactate regulates BDNF expression in the rat hippocampus. Our data revealed that increases in blood lactate concentration upregulate the hippocampal expression of BDNF and VEGF, two growth factors that contribute to the behavioral actions of antidepressants. We next examined whether lactate-induced expression of BDNF and VEGF was associated with an antidepressant-like behavioral response. We found that intraperitoneal injection of lactate decreases the immobility time in both the forced swim test and the repeated open-space forced swim test, an animal model of depression that responds to chronic, but not acute, antidepressant treatment. Together, these data provide evidence that intraperitoneal injection of lactate induces antidepressant-like behavioral effects in rodents.

99. Evaluation of redox dysregulation in the pathology of schizophrenia using induced pluripotent stem cell technology

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Background: 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.
Methods: 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.
Results: 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.
Conclusions: 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.

100. Differentiation between Parkinson disease and other forms of Parkinsonism using support vector machine analysis of susceptibility-weighted imaging (SWI): initial results

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Objectives: To diagnose Parkinson disease (PD) at the individual level using pattern recognition of brain susceptibility-weighted imaging (SWI). Methods: We analysed brain SWI in 36 consecutive patients with Parkinsonism suggestive of PD who had (1) SWI at 3 T, (2) brain 123I-ioflupane SPECTand (3) extensive neurological testing including follow-up (16 PD, 67.4±6.2 years, 11 female; 20 OTHER, a heterogeneousgroup of atypical Parkinsonism syndromes 65.2±12.5 years, 6 female). Analysis included group-level comparison of SWI values and individual-level support vector machine (SVM) analysis. Results: At the group level, simple visual analysis yielded no differences between groups. However, the group-level anal- yses demonstrated increased SWI in the bilateral thalamus and left substantia nigra in PD patients versus other Parkinsonism. The inverse comparison yielded no supra-threshold clusters. At the individual level, SVM correctly classified PD patients with an accuracy above 86 %. Conclusions: SVM pattern recognition of SWI data provides accurate discrimination of PD among patients with various forms of Parkinsonism at an individual level, despite the absence of visually detectable alterations. This pilot study warrants further confirmation in a larger cohort of PD patients and with different MR machines and MR parameters. Key Points: Magnetic resonance imaging data offers new insights into Parkinson's disease Visual susceptibility-weighted imaging (SWI) analysis could not discriminate idiopathic from atypical PD However, support vector machine (SVM) analysis provided highly accurate detection of idiopathic PD SVM analysis may contribute to the clinical diagnosis of individual PD patients Such information can be readily obtained from routine MR data.
Keywords: Parkinson disease . SWI .Brain iron deposition .
SVM . Early diagnosis

This paper has yet been published.

Other

101. Visual contrast sensitivity in schizotypy: better with negative schizotypy and worse with cognitive disorganisation

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Impairments in basic visual functions are common in patients with schizophrenia, and have also been observed in healthy individuals high in schizotypy. For visual backward masking, for instance, we observed relative deficits as a function of elevated cognitive disorganisation, but not as of negative or positive schizotypy (Cappe et al., 2012). Here, 81 healthy students (69 women) performed a contrast sensitivity task, i.e. observers indicated which of two intervals contained a low-contrast Gabor patch. All participants filled in the short version of the O-LIFE questionnaire.

High as compared to low cognitive disorganisation scores were associated with deteriorated detection, whereas high as compared to low introvertive anhedonia was associated with better detection performance. These results support previous observations that cognitive disorganisation is detrimental to basic visual functions. The finding that negative schizotypy goes along with enhanced basic visual performance requires replication, in particular because it might be more task-specific.

102. Protein oxidation 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 Alzheimer's and control's brain, were used to identify specific targets and to determine the influence of oxidative stress on protein expression especially the synaptic ones. Proteins were studied by 1D and 2D electrophoresis, by Coomassie blue staining, Western blots and immunostaining for different proteins of interest and also for post-translational modifications including S-nitrosylation, carbonylation, and ubiquitination. Carbonylated proteins were detected by derivatization of the carbonyl groups with dinitrophenylhydrazine (DNPH) and 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, S-nitrosylation and ubiquitination levels in Alzheimer's group compared to control group. 2D analyses of carbonylated proteins followed by MALDI/TOF detection showed an increase in the carbonylation levels of several proteins such as synaptic ones, cytoskeleton ones and certain proteins involved in glucose metabolism. In parallel, DIGE results showed an alteration of cystein oxidation between proteins from Alzheimer's and control's groups. Protein identification by MALDI/TOF showed that several types of proteins were affected and especially cytoskeleton ones. These results revealed an increase of oxidative stress during Alzheimer's disease which alters protein function and plays a major role in proteins accumulation, synaptic proteins loss and neuronal death.

103. The effects of stress on physiology, anxiety and cognition in socially-living rats

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Animal studies involving semi-natural environments provide a valuable approach to investigate key questions regarding the formation and bio-behavioral impact of social hierarchies. Stress was implicated in the formation of social hierarchies in rodents under laboratory standard conditions; however, little is known about stress effects in the dynamics of social hierarchies under semi-natural conditions. Here, we addressed this question in rats and investigated the consequences of stress and semi-natural environmental housing on physiological markers and behavioral anxiety. Long-Evans rats were either group-housed (4 males, 2 females) in Enriched-Environments (EE) or single-housed (SE) in standard cages. During the first days of cohabitation, half of the rats were briefly stressed. Social interactions were videotaped and subsequently analyzed to determine agonistic behaviors. Anxiety-like behaviors were assessed in the open-field test on day 10 of EE exposure. We found that stress induced anxiety-like behaviors and increased adrenal glands weight in SE but not in EE animals; but note that EE increased adrenal weight. Importantly, stress increased agonistic behaviors in EE animals during the first days of cohabitation. Altogether, our findings suggest that long-term effects of stress in physiological stress markers and emotionality observed under social isolation might be overridden by environmentally and socially complex contexts that seem to impinge, on their own, an allostatic load on the individuals. They also support the view that stress increases aggression in social groups.

104. AltitudeOmics: The effect of high altitude ascent and acclimatisation on cerebral blood flow regulation

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Adequate oxygen supply to the brain is critical to maintain brain function. Hypoxia presents a unique challenge in maintaining sufficient cerebral oxygen delivery (DO2). We assessed by ultrasound cerebral blood flow (CBF: internal carotid, vertebral arteries and middle cerebral artery velocity [MCAv]) and arterial blood pressure (index of cerebral autoregulation; CA) during rest and hypercapnic breathing (MCAv-CO2 slope; index of cerebrovascular function) in 21 healthy subjects at sea-level (SL) and upon arrival at 5260m (ALT1) and after 16 days of acclimatisation (ALT16). Cerebral DO2 was calculated as the product of arterial oxygen content (CaO2) and flow in each respective artery and summed to estimate global CBF. Global CBF increased ~70% upon arrival at ALT1 ($P<0.05$) and returned to SL values at ALT16 as a result of changes in cerebral vascular resistance. A reciprocal pattern in CaO2 maintained global cerebral DO2 across acclimatisation. MCAv-CO2 slope was elevated by ~79% upon arrival at ALT1 and further increased by ~89% at ALT16 ($P<0.05$). Indexes of CA were reduced upon arrival at ALT1 ($P<0.05$), but did not change with acclimatisation at ALT16 ($P>0.10$). Cerebral DO2 was well maintained upon acute exposure and acclimatisation to hypoxia. Cerebrovascular function was enhanced with acclimatisation to high altitude, but these changes did not mitigate the reduction in CA associated with hypoxic exposure.

105. Whole mount preparations for high resolution whole brain scanning

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The mammalian brain is composed of heterogeneous cell populations with particular distributions within and across brain regions. These cells in turn make synaptic connections and form intricate neural networks that span the entire brain. It has been a longstanding challenge to map this cellular complexity and their connectivity, especially across large brain structures or ultimately the entire brain.
We believe that classical microscopy is unsuitable for large scale brain mapping at cellular resolution because it requires time consuming and error prone tissue sectioning, imaging and reconstruction steps. Whole mount preparations, on the contrary, eliminate tissue losses, distortion and alignment errors by preserving the integrity of the sample. However histological and optical constrains have limited whole mount imaging to smaller and more transparent samples such as zebrafish, embryos and insect brains. Recent advances in clearing techniques have enabled the imaging of more opaque samples, such as the whole adult mouse CNS . Unfortunately image contrast and resolution have been insufficient to resolve anatomical fine detail.

We have combined advances in light sheet microscopy (LSM) and optimized histological treatment to obtain high-resolution whole mount rodent brain datasets. Fluorescent transgenic and dextranamine injected brains were imaged with confocal light sheet microscopy at micron-scale resolution with high image contrast. We find that this technique provides datasets well suited for quantification of anatomical features with cellular resolution across the entire brain. This paves the way for a wide range of novel physiological and pathological experimental paradigms, which have hitherto been unapproachable.