UNIVERSITAS FRIBURGENSIS

BENEFRI

Neuroscience

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# Workshop 2014

# Human Brain Research and Animal Models

January 21-23, 2014
Department of Biology, University of Fribourg
0.110 Auditorium Plant Biology / Anatomy Hall
Rte A. Gockel 3
CH-1700 Fribourg

January 21th, Tuesday

**Morning session: "fMRI IN COGNITIVE RESEARCH"**
**Chair: Roberto CALDARA and Jean-Marie ANNONI**

08:40 Welcome Address
**Marco** R. **CELIO**

08:45-9h:35 "Principles of Voxel Based Morphometry and Diffusion Tensor Imaging"
**Roberto CALDARA**, Fribourg

09:35-10h:10 "fMRI in language Research"
**Jean-Marie ANNONI**, Fribourg

10:10-10:30 *Coffee Break*

10:30-12:30 "Workshop of fMRI Analysis with SPM"
**Michael MOUTHON**, Fribourg (room B230 of the building Pérolles 2)

12:30-13:30 *Lunch*

13:30-14:15 *Poster session 1 (Posters 1 to 6, 8 and 17)*

**Afternoon session: "INSIGHTS INTO REHABILITATION"**
**Chair: W. TAUBE & J-P. BRESCIANI**

14:15-14:30 Short talk
**Marathe Swananda**, PhD Student (Poster 20)

14:30-15:30 "The mirror paradigm: theoretical and clinical contribution"
**Michel GUERRAZ**, Université de Savoie

15:30-15:45 *Coffee Break*

15:45-16:45 "Neurobotics: from neuroscience to robot-assisted assessment and neurotherapy"
**Roger GASSERT**, ETH Zürich

January 22, Wednesday

**Morning session: "NEUROBIOLOGY OF NON-MAMMALIAN ANIMAL MODELS"**
**Chair: Dominique GLAUSER, Claire JACOB**

09:00-09:15 Introduction: Studying neural development and function in non-mammalian model organisms
**Dominique GLAUSER**

09:15-10:15 "The sensory physiology of survival tactics in arthropod vectors of disease"
**Patrick GUERIN, Institute of Biology, University of Neuchatel**

10:15-10:30 *Coffee Break*

10:30-11:30 "Time flies - neural mechanisms of learning and processing of fast olfactory information"
**Giovanni GALIZIA, Biology, University of Konstanz**

11:30-12:30 "Analysis of neuronal circuit structure and function in zebrafish"
**Rainer FRIEDRICH, Friedrich Miescher Institute, Basel**

12:30-13:30 *Lunch*

13:30-14:15 *Poster session 2 (Posters 7, 9 to 14)*

**Afternoon session: "NEUROBIOLOGY OF NON-MAMMALIAN ANIMAL MODELS"**
**Chair: Boris EGGER**

14:15-14:30 Short talk
**Oriane Guillermin,** PhD Student (poster 22)

14:30-15:30 "Optogenetic analyses of synaptic transmission and neural networks generating behavior in *C. elegans"*
**Alexander GOTTSCHALK, Institute of Biochemistry, University of Frankfurt**

15:30-15:45 *Coffee Break*

15:45-16:45 "Cellular and molecular mechanisms of asymmetric cell division"
**Clemens CABERNARD, Biocenter University of Basel**

January 23, Thursday
**Morning session: "DYNAMIC ASPECTS OF CORTICAL FUNCTION IN NON-HUMAN PRIMATES"**
**Chair: Gregor RAINER & Eric SCHMIDLIN**

09:05-09:10 Introduction
**Gregor RAINER**

09:10-10:10: "Context-dependent computations by recurrent dynamics in prefrontal cortex"
**Valerio MANTE,** ETZ Zürich

10:10-10:25 *Coffee break*

10:25-11:25: "Temporal and predictive processes in motor cortex"
**Alexa RIEHLE,** CNRS Marseille

11:25-12:25: "When motor cortex is active"
**Alexander KRASKOV,** UCL London

12:30-13:30 *Lunch*

13:30-14:15 *Poster session 3 (Poster 15 to 22)*

**Afternoon session: "RODENT MODELS TO INVESTIGATE BRAIN FUNCTION"**
**Chair: Beat SCHWALLER & Lavinia ALBERI**

14:15-14:30 Short talk
**Valerie Bruegger**, PhD Student **(Poster 7)**

14:30-15:30 "Molecular mechanisms of regulated neurogenesis".
**Verdon TAYLOR**, Uni Basel

15:30-15:45 *Coffee Break*

15:45-16:45 "Use of viral vectors to model neurodegenerative disorders and explore targets for disease-modifying treatments"
**Bernard SCHNEIDER**, EPFL Lausanne

16.45 End of the symposium
**Marco R. CELIO**

**POSTER 1**

**Sensitivity of communicability metrics in the case of lesions in the brain structural network.**

J. Andreotti [1], K. Jann[1,2], L. Melie-Garcia[3,1], T. Dierks[1], A.Federspiel[1]

1. Department of Psychiatric Neurophysiology, University Hospital of Psychiatry, University of Bern, Bern, Switzerland 2. Department of Neurology, Ahmanson-Lovelace Brain Mapping Center, University of California Los Angeles, USA3. Neuroinformatics Department, Cuban Neuroscience Center, Havana,Cuba

**Purpose:** Computational network analysis offers new tools to quantify and analyze connectivity in brain structural networks. In our analysis, changes in the topology of brain structural networks in the case of simulated lesions are characterized by the use of several network metrics [2]. In particular, communicability related metrics have been included in the analysis ([3],[4]), as they account for indirect paths that may become more important in case of lesions.

**Methods:** Nineteen healthy subjects underwent two consecutives diffusion tensor imaging sequences. In addition, T1-weighted images were acquired to obtain a cortical parcellation and define the nodes of the network. Each region (ROI) of the parcellation was used as seed region for probabilistic tractography and an edge between two nodes existed if a nonzero connectivity index was found between the correspondent ROIs. The edge weight was defined as the proportion of streamlines connecting the two nodes corrected by their volume [1]. For each of the subjects, one network was used as baseline, while the other was damaged by simulated lesions. Lesions are simulated by partially or completely removing a node or an edge.

The aims of the analysis were the comparison of the different metrics to detect nodes sensitive to lesions and the evaluation of local changes in the network metrics in the case of lesions.

**Results:** Measures of strength and communicability were the best to select sites for single attacks; also communicability was the best to select a subset of nodes sensitive to lesions (Perm test: $p<0.0014$). In addition, communicability related metrics were found to be more sensitive to random edges lesions and local changes were found also in regions distant from the focus of the lesions.

**Discussion:** Communicability is a wider measure of connectivity based on the idea that all the paths connecting two nodes contribute to the information flow ([3],[4]). Secondary and longer paths may be strengthened in the case of lesions. Our results suggest that communicability related metrics are sensitive to changes in the brain structural network topology in the case of lesions.

**References:** [1] Iturria-Medina Y. et al., *NeuroImage* 2007 [2] Rubinov M. and Sporns O. *NeuroImage* 2010 [3] Estrada E. and Hatano N. *Phys. Rev.* 2008 [4] Crofts J. and Higham D. *J. R. Soc. Interface*. 2009

**POSTER 2**

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

Simon Badoud (2, 5), Duy Nguyen (3), Isabelle Barnaure (1), Marie-Louise Montandon (4), Karl-Olof Lovblad (1), Eric M. Rouiller (5), Pierre R. Burkard (2), Sven Haller (1)

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*2) Department of Neurology, Geneva University Hospitals and Faculty of Medicine, University of Geneva, Switzerland*

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*4) Nuclear medicine and molecular imaging unit, DISIM, Geneva University Hospitals and Faculty of Medicine, University of Geneva, Switzerland*

*5) Unit of Physiology and Program in Neurosciences, Department of Medicine, Faculty of Sciences, University of Fribourg, Chemin du Musée 5, CH-1700 Fribourg, Switzerland.*

**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 $^{123}$I-ioflupane SPECT and (3) extensive neurological testing including follow-up (16 PD, 67.4 ± 6.2 years, 11 female; 20 OTHER, a heterogeneous group 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 analyses 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.

**POSTER 3**

**Perception of co-speech gestures during dialogues: Evidence for altered gaze patterns in aphasic patients**

Basil C. Preisig1, Noëmi Eggenberger1, Giuseppe Zito3, Rahel Schumacher1, Simone Hopfner1, Tim Vanbellingen1,4, Thomas Nyffeler1,4, Klemens Gutbrod2, Claudio L. Bassetti1, and René M. Müri1,2

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3ARTORG Center for Biomedical Engineering Research, University of Bern, Switzerland
4Center of Neurology and Neurorehabilitation Center, Luzerner Kantonsspital, Switzerland

**Background:** Aphasia is an acquired language disorder that occurs generally after left-hemispheric brain damage. Since patients suffering from aphasia are restricted in their verbal abilities, they may compensate their verbal deficits by using gestures. Previous studies have shown that some patients could use gestures as compensatory strategies, while others did not. In contrast to previous research which focused mainly on gesture production, the present study investigated the perception of co-speech gestures in aphasic patients. We expected that aphasia influences gaze behavior in patients and that altered gaze patterns would be associated with content-related comprehension.
**Methods:** 20 aphasic patients and 20 healthy control subjects matched for age, sex, and education were included in the study. Gaze data was collected by means of a contact-free infra-red eye tracker while subjects were watching videos of dialogue situations. For data analysis, a region of interest (ROI) analysis was conducted.
**Results:** In line with previous findings, we found that subjects rather gazed at the face of the speaking interlocutor than at the gesturing hand. Most interestingly, we found main effects of gesture, group and a ROI x group interaction. Subjects tended to look less at the face and fixated more on the actor's hands during the presence of a co-speech gesture. Overall, aphasic patients gazed less at the face and tended to look more on the hands compared to healthy controls. Further, we found a trend for an association between the time spent looking at the face and content-related comprehension.
**Conclusion:** The face is the main attractor for somebody who is following a dyadic conversation. However, the presence of co-speech gestures seems to elicit a partial shift of the attention to the gesturing hand. As expected, we could show that aphasic patients display altered gaze patterns. They tended to fixate less on the face, a finding that might be related to language comprehension.
**Keywords:** Aphasia, gesture, gaze, dialogue, eye tracking

**POSTER 4**

**A MATLAB based eye tracking control system using non-invasive helmet head restraint in the macaque.**

Mohamed Faiz Bin Mohamed Mustafar[1], Paolo De Luna & Gregor Rainer[1]

1. Department of Physiology/Medicine, University of Fribourg.

The magnetic search coils approach in visual psychophysics and behavioral experiment remarks a milestone in visual science research. However, today non-invasive methods seems to provide a promising alternative to this gold standard method in measuring eye movement in certain application. In this paper we developed a MATLAB-based software solution for the non-invasive eye-tracking in non-head restrained non-human primate. This system allows for data collection from the eye tracker for online control and storage, visual target display, monitoring of fixation, reward delivery and provide feedback of the current eye position. The distinctive feature of this system if that it relies on the data streaming mode which enables the system to sample the eye position data high temporal accuracy without redundancy. The result reported comparable performance in terms of stability, accuracy and validity with the rigid head-posted approach.

**POSTER 5**

**The coaxial PV1-Foxb1-nucleus projects to the PAG**

A. Bilella[1], G. Alvarez-Bolado[2] , M. R. Celio[1]

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The PV1-nucleus is a cord-like structure comprised of parvalbumin-positive neurons lodged within the ventrolateral hypothalamus [1-3]. Indipendently, a stream of Foxb1-expressing neurons migrating to the ventrolateral hypothalamus was also described [4, 5]. We have found that parvalbumin-positive and Foxb1-expressing neurons intermingle together in the PV1-nucleus which, on the base of this discovery, has recently been redesigned as the PV1-Foxb1-nucleus (Bilella et al. in press).

We mapped the efferent connections of PV1-Foxb1-nucleus using Cre-dependent viral constructs stereotactically injected in Foxb1-Cre and parvalbumin/Foxb1-Cre mice.

The PV1-Foxb1-nucleus projects in two different directions, to a lesser extent in the prefrontal cortex rostrally, and in the periaqueductal grey (PAG) and hindbrain, caudally.

The main projections sprout in two different bundles and reach the dorsolateral and the ventrolateral [6] portion of the PAG. The connections between the lateral hypothalamic area and the PAG could be involved in several activities as modulating pain circuits and paves the way for further investigation to highlight important, yet undiscovered functions of the PV1-Foxb1-nucleus.

Literature

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2. Girard, F., et al., *Gene expression analysis in the parvalbumin-immunoreactive PV1 nucleus of the mouse lateral hypothalamus.* Eur J Neurosci, 2011. **34**(12): p. 1934-43.
3. Meszar, Z., et al., *The lateral hypothalamic parvalbumin-immunoreactive (PV1) nucleus in rodents.* J Comp Neurol, 2012. **520**(4): p. 798-815.
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5. Zhao, T., et al., *Genetic mapping of Foxb1-cell lineage shows migration from caudal diencephalon to telencephalon and lateral hypothalamus.* Eur J Neurosci, 2008. **28**(10): p. 1941-55.
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**POSTER 6**

**Notch1 activity in mitral cells is odor dependent and contributes to olfactory behavior.**

Emanuele Brai[1], Lavinia Alberi [1]

1. University of Fribourg, Department of Medicine, Anatomy Unit

It has been previously shown that Notch signaling plays an important role in synaptic plasticity, learning and memory functions both in Drosophila and rodents. In this paper, we report that this feature is not restricted to hippocampal networks but also interests the olfactory bulb (OB). Olfaction and odor discrimination in rodents are innate and essential for survival. Notch1 expression is enriched in mitral cells of the mouse OB. These principal neurons are responsive to specific input odorants and project directly to higher brain structures. Olfactory stimulation activates a subset of mitral cells, which show increase in Notch activity. Notch1cKOKIn mice display altered c-fos expression and decreased aversion to propionic acid as compared to wildtype controls. Extracellular recordings in the mitral cells layer in Notch1cKOKIn and wildtype mice show that Notch1 regulates the magnitude of the neuronal response to olfactory stimuli. This indicates, for the first time, that Notch1 is involved in olfactory processing and contributes to olfactory behavior.

**POSTER 7**

**Functions of histone deacetylases in Schwann cells during regeneration**

Valérie Brügger[1], Sophie Ruff, Céline Pattaroni, Patrick Matthias, Ueli Suter, Claire Jacob

1. University of Fribourg, Department of Biology

To minimize metabolic expenses while maintaining rapid conduction, axons are surrounded by myelin sheaths. These sheaths are formed by glial cells called Schwann cells in the peripheral nervous system (PNS) and oligodendrocytes in the central nervous system (CNS). Schwann cells play a key role in PNS regeneration. Indeed, they can efficiently promote axonal regrowth, due to their capacity to de-differentiate and re-differentiate after a lesion, whereas oligodendrocytes in the CNS cannot.

Histone deacetylases (HDACs) are key transcriptional regulators that control gene expression by remodeling chromatin and modifying the activity of transcription factors. There are 18 known mammalian HDACs, subdivided into four classes. Using mouse genetics, we have previously shown that the two highly homologous class I HDACs HDAC1 and HDAC2 are crucial for survival and myelination of Schwann cells. Our data indicate that these two HDACs are also required for the maintenance of peripheral nerve integrity in adults. Our current aim is to understand whether and how HDACs can influence the regeneration process in Schwann cells.

We found that several HDACs, including HDAC1 and HDAC2, were strongly upregulated during regeneration after a sciatic nerve crush lesion in adult mice, suggesting important functions in this process. To analyze the potential functions of HDAC1 and HDAC2 in Schwann cells during regeneration, we generated a tamoxifen-inducible conditional knockout mouse line where we ablated HDAC1 and HDAC2 in adult mice specifically in Schwann cells. In the absence of HDAC1 and HDAC2, Schwann cells de-differentiated faster after lesion, and remyelination was thinner. Consistently, the key transcription factor of differentiation Krox20 and the major component of the myelin sheath myelin protein zero (P0) were strongly reduced 12 days and 1 month post crush lesion, respectively, when Schwann cells start to re-differentiate and to rebuild myelin sheaths.

We are currently investigating the molecular mechanisms responsible for these functions.

**POSTER 8**

**Lexical processing of written words is reinforced by non-lexical networks in shallow but not deep orthography**

Karin A. Buetler[1], Diego de León Rodríguez[1], Marina Laganaro[2], René Müri[3], Lucas Spierer[1] and Jean-Marie Annoni[1]

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Referred to as orthographic depth, the degree of consistency of grapheme/phoneme correspondences varies across languages from high in shallow orthographies to low in deep orthographies. The Orthographic Depth Hypothesis (Katz & Feldman, 1983) posits that during reading, shallow orthographies may favor non-lexical pathways, whereas deep orthographies may favor lexical pathways to map graphemes and phonemes. Consistently, in a previous study, we found a modulation of the routine non-lexical pathways engaged in pseudoword reading depending of the orthographic depth of language context. In the present study, the aim was to extent these findings by investigating the impact of orthographic depth on reading route selection in word reading. To address this question, we analyzed high density 128-channel electroencephalography responses to words in a deep (French) and shallow (German) language that were presented to highly proficient bilinguals. Electrical neuroimaging analyses of event-related potentials to German and French word reading revealed a significant topographic modulation 230-300ms post-stimulus onset, indicative of distinct brain networks engaged in reading. The brain sources underlying these topographic effects were located within left dorsolateral, inferior frontal and insular regions (German>French), previously associated to non-lexical processing. These collective results support the orthographic depth hypothesis, by showing that reading in a language with consistent grapheme/phoneme correspondences (German) was associated to a stronger engagement of non-lexical pathways than reading in a language with inconsistent grapheme/phoneme correspondences (French). The absence of a modulation of lexical pathways suggests that they are equally engaged in familiar word reading across languages. Thus, the lexical pathways generally engaged in word reading are reinforced by non-lexical networks in the shallow but not deep orthography.

**POSTER 9**

**Metabolic disorders of the brain in dogs with hepatic encephalopathy detected with $H^1$-MR Spectroscopy**

Inés Carrera, Dieter Meier, Patrick Kircher, Henning Richter, Matthias Dennler

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Graduate School for Cellular and Biomedical Sciences, University of Bern, Switzerland (Carrera).

Institute for Biomedical Engineering, University & ETH Zurich, MR Zentrum USZ, 8091 Zurich, Switzerland (Meier)

Hepatic encephalopathy (HE) is a multifactorial neurological condition associated with failure of the liver to detoxify inhibitory neurotoxins. Ammonium plays a central role in the development of the encephalopathy. Astrocytes are the site of ammonia detoxification in the brain and eliminate ammonia by the synthesis of glutamine through amidation of glutamate by glutamine synthetase. High concentration of glutamine causes astrocytes to swell and consequent brain edema. Proton Magnetic Resonance Spectroscopy (H-MRS) allows the determination of brain metabolites in a non-invasive way. The purpose of this study was to investigate the metabolic disorders of the brain in dogs with hepatic encephalopathy, compared to a control group.

Materials & Methods: 6 dogs were included with hepatic encephalopathy (HE) and 12 control dogs. Neurological examination and complete laboratory work up were included. MRI and MRS examinations were performed with a 3 scanner. MRI included standard sequences. MRS was performed using a single voxel, PRESS 35, in the area of the basal ganglia. The metabolites analyzed included Glx (the sum of glutamate and glutamine), mI (myo-inositol), NAA (N-acetyl aspartate), Cho (choline) and Cre (creatine). The data was analyzed with LCModel. Man-Whitney-U–test checking for normality and independent two-sided t-test were performed.

Results: Specific changes were noted in the HE group, which included elevated Glx and reduced mI ($p=0.0001$). Cho and NAA were also slightly reduced on the HE groups compared to the control group. No differences were noted in the Cre concentration. In conventional MR images brain atrophy was noted in 4/6 dogs, without any other abnormalities seen.

Discussion: H-MRS allows accurate diagnosis of HE in dogs, and confirms the principal role of ammonium in the pathogenesis of the disease. Detection of subclinical HE and monitoring of the disease after treatment, are important clinical situations were H-MRS will be very useful.

**POSTER 10**

**Cortical circuits matching body metabolic signals and behavior.**

Isabel De Araujo Salgado & Christophe Lamy

Department of Medicine, Unit of Anatomy, University of Fribourg

The insular cortex (IC) monitors the homeostatic state of the body and responds to peripheral metabolic challenges, such as fasting. Studies in humans and animal models have shown that it also plays a key role in complex behaviors, such as decision making and emotions. However, the neuronal circuits involved in these integrative functions of IC are poorly understood. We aim to investigate the cellular mechanisms implicated in the monitoring of body metabolic states by IC and to identify the cortical microcircuits that link these mechanisms with complexes behaviors. Whole-cell electrophysiological recordings from acute slices of mouse IC combined with histological techniques enabled us to characterize the biophysical, morphological, and molecular identity of IC neurons and their patterns of responses to metabolic signals. A subpopulation of IC neurons was sensitive to changes in extracellular glucose concentrations with either a glucose-inhibited or a glucose-excited phenotype. We further showed that glucose responsiveness is an intrinsic property of some of these cells. We are now looking at the cellular mechanisms involved in these responses.

**POSTER 11**

**Adaptation to Incomitant Vergence Disparity**

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[#] Graduate School for Cellular and Biomedical Sciences, University of Bern, Switzerland

**Purpose**

Vergence movements are slow disconjugate eye movements which may be triggered by image disparity or accommodation. There exist numerous clinical contexts where image disparity may vary with the direction of gaze. A common example is a sixth cranial nerve palsy with increasing image disparity in gaze toward the affected muscle. Adaptive changes to such incomitant image disparity have been poorly investigated and are the scope of this study.

**Methods**

Vergence stimuli of gaze dependent magnitude were used to mimic the image disparity of an incomitant strabismus. In a first experiment prisms were placed such that stimuli were viewed through the prisms in one gaze direction but not in the other gaze directions. In a second experiment we used a haploscope to modify image disparity according to gaze. We measured vergence responses that were made after a saccade shifting gaze from left to right, with increased image disparity in right gaze. We analysed changes of rise time or mean velocity, latency, and amplitude over time.

**Results**

Increased image disparity in right gaze led to a decrease of vergence rise time and latency within minutes. Using the haploscope to deliver vergence stimuli, we again found a significant increase in vergence kinetics (mean velocity), but not in latency.

**Conclusion**

In this study we show that repetitive increase of the vergence demand leads to rapid improvement of the vergence response kinetics with a moderate effect on the latency. This type of vergence plasticity helps to rapidly restore stereovision after a saccade is made into a field of gaze with increased image disparity.

**POSTER 12**

**Visual exploration of co-speech gestures in aphasic patients: An eye-tracking study**

Noëmi Eggenberger[1], Basil C. Preisig[1], Giuseppe Zito[2], Simone Hopfner[1], Tim Vanbellingen[1], Rahel Schumacher[1], Thomas Nyffeler[1,4], Klemens Gutbrod[3], Claudio L. Bassetti[3], and René M. Müri[1,3]

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**Introduction**: Gesturing, which includes co-speech gestures, is a crucial part of human communication. Healthy participants spend about 88-95% of the time fixating a speaker's face, while only a minority of fixations is directed at gestures. However, it is unclear whether aphasic patients display similar patterns. The present study aimed to investigate the visual exploration of co-speech gestures in aphasic patients.

**Subjects and Methods:** 20 aphasic patients and 20 controls participated in this study.

75 short video sequences in three experimental conditions that varied in the level of congruity between speech and gestures were created. After each sequence, participants had to judge this congruity by keypress.

A remote eye-tracking device allowed comfortable gaze tracking and off-line analysis of parameters such as fixation duration on predefined areas of interest (AOIs).

**Results:** Repeated measures ANOVAs were performed for cumulative fixation duration (the total time a specific AOI was fixated). This yielded a significant interaction between the factors AOI * Group, indicating that aphasic patients spent more time fixating the hands compared to healthy controls, while healthy controls fixated more on the speaker's face compared to the patients.

**Discussion:** In line with previous research, all participants spent most time fixating the speaker's face. Aphasic patients showed an altered visual exploration behavior insofar as they looked less on the face but more on the gesturing hands compared to controls. Aphasic patients might thus rely more on the additional (nonverbal) information presented by gestures in order to understand verbal utterances and to judge increasingly complex sequences. It could also be assumed that the visual attention of aphasic patients is more strongly influenced by bottom-up information processing, such as gestural movements that attract attention unconsciously.

**Keywords:** Aphasia, gestures, perception, eye-tracking

**POSTER 13**

**The putative role of parvalbumin in Autism Spectrum Disorders**

Federica Filice[1], Beat Schwaller[1]

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Autism spectrum disorders are largely neurodevelopmental disorders with a strong genetic component and are characterized by three core symptoms: (1) impairments in social interaction and (2) communication; (3) restricted, repetitive and stereotyped patterns of behavior, interests, and activities. It has been shown that genes associated with autism (NLGN3, 4, Shank1,2,3) encode proteins subjected to activity-dependent changes in neuronal function and participate in processes such as synaptic formation, maturation elimination and plasticity. The dysregulation of this activity - dependent signaling networks controlling synapse development and function may be an important component of the molecular basis of ASD, but alternative explanations must be considered, such as an impairment of neurotransmission, i.e. excitation/inhibition (E/I) balance or defects in earlier steps in nervous-system development. In this scenario, interneurons play a key role in the maintenance of the global balance of activity in cortical networks; evidences have been provided that interneuron dysfunctions are linked with cognitive impairment in neuropsychiatric disorders. In particular, the number of fast-spiking interneurons (FSI) expressing the calcium-binding protein parvalbumin (PV) has been reported to be decreased in different well-assessed mouse models of ASD.

According to the current view, this decrease in PV-immunoreactive (PV-ir) cells is due to a “loss” of PV-expressing FSI, leading to a change in the E/I balance that may be related to ASD. Yet, alternative explanations need to be considered, such that the putative “loss” of PV-ir neurons in ASD mice models might be the result of a reduction in PV expression or synthesis. Of interest, PV-deficient mice (PV-/-) show ASD-like symptoms as reported in other “canonical” ASD mouse models. Here, we set out to determine whether the number or density of “PV FSI” is altered in PV-/- mice using stereological methods. Initial results indicate the number of “PV-interneurons”, is not altered in PV-deficient mice. Thus, a mere down-regulation of PV affecting the spatiotemporal aspects of FSI intracellular Ca2+ signals appears to be sufficient to precipitate in an ASD-like behavioral phenotype.

**POSTER 14**

## Inverse correlation between white matter cerebral blood flow and structural connectivity of the human brain

S. Giezendanner[1], M. Fisler[1], L. Soravia[1], J. Andreotti[1], S. Walther[1], R Wiest[2], T Dierks[1]1 , A Federspiel[1]

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2) University Institute of Diagnostic and Interventional Neuroradiology, Inselspital and University of Bern, Bern, Switzerland

**Introduction:** Cerebral blood flow (CBF) is crucial for neuronal processes in the brain. However, little is known about white matter perfusion and its relation to structural connectivity. Recently, an inverse correlation between white matter CBF and structural connectivity was reported on a tract-specific basis [1]. In the present study we present a voxel-wise approach to probe for a relationship between metabolic and microstructural connectivity in white matter across subjects.

**Methods:** A total of 32 healthy subjects were included in the study (mean age: 28.7 years ± 8.2). All MRI scans were performed on a 3T Siemens TRIO TIM scanner. Diffusion tensor imaging (DTI) was performed with a spin echo EPI along 42 non-collinear directions. Preprocessing of diffusion tensor images was carried out with TBSS [2], part of FSL [3].
Pseudocontinuous ASL (pCASL) sequence was acquired with a tagging duration of 1720 ms and a postlabeling delay of 1100 ms resulting in a time-series of each 50 control and label images [4, 5]. Preprocessing of ASL data was carried out with BASIL [6] part of FSL [3].
CBF images were co-registered to fractional anisotropy (FA) maps and subsequently the nonlinear warps and skeleton projections from the TBSS preprocessing were applied to the CBF images. A voxel-wise correlation analysis between FA and CBF skeleton maps over all subjects was performed with the randomise program [7], part of FSL [3].

**Results:** A significant negative correlation (*corr p* <0.05) was observed between CBF and FA values in the body of the corpus callosum, the right anterior thalamic radiation, the right anterior corona radiata and the forceps minor. Furthermore, a significant positive correlation (*corr p* <0.05) was found between CBF and radial diffusivity in the genu and the body of the corpus callosum, the forceps minor, the right anterior corona radiata and the right thalamic radiation. All results are corrected for multiple comparisons and used a threshold-free cluster enhancement.

**Conclusions:** The present study investigated perfusion and microstructural properties within white matter across subjects and showed a significant relationship between CBF and microstructural properties. These findings are in line with a previous study probing the same parameters on a tract-specific basis [1]. Our findings indicate an inverse relationship of WM perfusion and its structural connectivity. This inverse relationship suggests the possibility that subjects with lower white matter perfusion display higher myelination, lower axonal diameter or more mechanical tightness within fiber bundles [1].

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**POSTER 15**

## Severity of neglect may increase with motion - insights from a touchscreen-based cancellation task

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**Background and Purpose:** In stroke patients, diagnosis of neglect is often made by paper-pencil cancellation tasks. These tasks entail static stimuli, and provide no information concerning possible changes in the severity of neglect symptoms when patients are confronted with motion. The identification of specific clinical characteristics, alerting clinicians about a possible worsening of neglect symptoms in the presence of motion, would thus be desirable.

**Methods:** Twenty-five patients with left spatial neglect after right-hemispheric stroke were tested with a new touchscreen-based cancellation task. This task allows to directly contrast the cancellation behaviour under a static (targets are static) and a dynamic (targets move on a random path) condition. Since visual field deficits are often found after a brain lesion, the integrity of the optic radiation was considered as an additional factor.

**Results:** In neglect patients with additional damage to the optic radiation, the severity of neglect significantly increased in the dynamic condition. In neglect patients with an intact optic radiation, no difference in the cancellation behaviour between the static and dynamic conditions was found.

**Conclusion:** In stroke patients with neglect, it is important to specifically assess whether a damage of the optic radiation is also present, since these patients may show a deterioration of their neglect symptoms in daily life when confronted with motion.

**POSTER 16**

## Emotional Rivalry: Homeostatic Emotions are Prioritized over Competing Sensory Emotions

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The ability to experience a wide variety of emotions is a fundamental characteristic of mankind. Hunger for food, air, and fluids (i.e. thirst) are examples of homeostatic emotions crucial for human survival, while sensory evoked emotions, such as anxiety and disgust, improve survival prospects when confronted with specific circumstances. In daily life, homeostatic and sensory emotions can be experienced simultaneously, which leads to an emotional conflict. We investigated the behavioural consequences of this emotional rivalry and its neurobiological underlying in subjects who experienced thirst (homeostatic emotion) and disgust (sensory emotion) at the same time. After 18 hours of water deprivation 20 healthy subjects underwent functional MR imaging. BOLD fMRI was measured during an intense thirst phase and after drinking to satiation. Both during thirst and satiation two odour stimuli (1 disgusting, 1 pleasant) were presented to the subject inside the scanner in an event related paradigm using an airflow olfactometer. Subjects rated both odours for pleasantness and intensity. For the fMRI data analysis a two-stage mixed effects model was calculated: At single subject level, we estimated the parameters of a GLM that included the odour stimulation during both hydration states. These parameter estimates were subsequently used in a random effects analysis, which was performed to identify disgust-related brain regions and brain areas related to the interaction between thirst and disgust. Comparing the odour ratings of the two hydration states, we found that the disgusting odour was rated as less repulsive in the thirsty condition, whereas no difference was found for the positive odour. The disgusting odour stimulation elicited neural activation in well-known disgust related brain areas, mainly in the anterior insula bilaterally. In the thirsty condition, this disgust-related activity was reduced in the left insular cortex. These results indicate a hierarchical processing of emotions in a situation of emotional rivalry: the homeostatic emotion thirst is prioritized, which is vital in terms of natural selection and determining human behavioural responses.

Homeostasis, Disgust, Thirst, Olfaction, fMRI, Insula

**POSTER 17**

# Transcriptome analysis of sleep deprivation associated neuroprotection in a rodent model of stroke

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## Background

Sleep-wake disturbances are frequent after stroke and they are linked with poorer rehabilitation and long-term outcome. Sleep deprivation (SD) and sleep disruption during the acute phase of stroke aggravate brain damage, however, when SD is performed prior to cerebral ischemia it results in neuroprotection with an effect similar to a preconditioning treatment. The mechanisms involved are not well understood and probably involve multiple molecular pathways. The main aim of this study was to identify which genes are involved in the neuroprotective mechanisms elicited by SD preconditioning through the use DNA oligonucleotide microarrays.

## Methods

A microarray study of gene expression was performed in adult Sprague-Dawley rats (n = 16). Animals were assigned to four experimental groups: 1) TSD.Is: total SD (TSD) performed before occlusion of the focal middle cerebral artery (MCAo); 2) nSD.Is: MCAo performed without previous SD; 3) TSD.Sham: TSD performed before sham surgery ; 4) nSD.Sham: sham surgery performed without previous SD. SD was performed during the last 6h of the light period by gentle handling and ischemia was induced immediately after. All animals were sacrificed 3 days following the MCAo/Sham surgery and gene expression in the lesioned hemisphere was analyzed . Data were evaluated by means of the Ingenuity Pathway Analysis. Quantitative Real-time PCR on genes of interest was performed in order to confirm microarray results and to assess gene expression in the contralateral hemisphere.

## Results

Stroke induced an upregulation of gene expression (74% of total modified genes) in the ischemic hemisphere compared to Sham animals. SD resulted instead in a pronounced gene downregulation (84% of total modified genes). Compared to nSD.Is, TSD.Is animals showed transcriptional changes in genes involved in cell cycle checkpoint regulation and immune response. Moreover an upregulation of genes involved in the neuroendocrine pathway was also observed. This pathway have never been described for other forms of preconditioning and includes: melanin concentrating hormone (MCH) glycoprotein hormones-α-polypeptide (CGA), hypocretin (HCRT), observed in TSD.Is animals compared to nSD.Is

## Discussion

Sleep deprivation before stroke might induce neuroprotection through the interaction of several pathways. The biological functions that seem to be mainly involved are:

- G1/S cell cycle checkpoint: these responses mimic neuroprotective strategies seen in hibernation and other hypoxia-tolerant states which lead to reversible “cellular arrest” and therefore to the inhibition of the progression of brain damage.
- Inflammatory system: the inhibition in inflammation could lead to the reduction of several agents including reactive oxygen radicals, nitric oxide, lymphotoxin, and other kind of cytokines involved in neuronal damage.
- Neuroendocrine system: the upregulation of pmch, Hcrt and CGA genes could mediate neuroprotection by the modulation of estradiol levels, a hormone which is already known for its protective effect in cerebral ischemia.

**POSTER 18**

## Reduced Ultrasonic Vocalizations in Rats after a Kainic Acid-Induced Lesion of the PV1-Foxb1 Nucleus

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We are currently investigating the function of a newly detected nucleus[1] (PV1-Foxb1, as neurons express either parvalbumin [PV] or Foxb1)[1,2] in the ventrolateral tuberal hypothalamus of mice and rats. Based on its location within the medial forebrain bundle as well as on its projection into the ventrolateral periaqueductal grey[3], we hypothesize an involvement of the PV1-Foxb1 nucleus in the regulation of the expression of emotions (vocalizations), or emotion-related vegetative effects (blood pressure, pain sensation). To test the hypothesis, whether PV1-Foxb1 plays a role in the expression of emotions, a group of adolescent Wistar rats was tickled as described elsewhere[4]. It is well known that tickling is a positive reinforcer that can induce positive affect in socially isolated rats[5], which will thereupon emit ultrasonic vocalizations in a frequency range around 50 kHz (positive USV).

Twelve Wistar rat pups were weaned after 3 weeks of age and housed individually during 4 weeks, in which each rat underwent a tickling session on Mondays, Tuesdays and Wednesdays. After a baseline period consisting of the first two weeks, test animals (n=8) received a bilateral stereotactic injection of kainic acid into the region of the PV1-Foxb1 nucleus. Control animals received either a bilateral stereotactic injection of saline into the same area (n=2) or just a comparable cut and suture of the skin (n=2) in order to blind the tickling experimenter to the treatment allocation. During all tickling sessions, USV were recorded using specialized equipment (Avisoft Bioacoustics) and rat behavior was recorded using a regular video camera. After perfusion, the number of PV-immunoreactive (PV-ir) cells that remained in the PV1-Foxb1 nucleus of every rat was estimated from fluorescence micrographs. Based on PV-ir cell numbers, test animals were classified as successful or mediocre lesions. In a group of 5 rats, clearly classified as successful lesions, the number of positive USV fell to almost zero during the first four tickling sessions after the treatments, whereas it remained relatively constant in the group of the mediocre lesions and even continued to increase in the two control groups (suture, saline). Overall, there was a correlation between the total number of PV-ir cells counted and the treatment-associated change in the number of positive USV. Positive correlations between treatment-associated changes in the number of positive USV and changes in further measures of “positivity”, basically representing a rat’s approach behavior towards the experimenter’s hand that had tickled them, were also found.

These results suggest a role of the lesioned structures in the expression of vocalizations. As axons of the medial forebrain bundle, passing through the PV1-Foxb1 nucleus, are not expected to express kainate receptors, the neurons making the PV1-Foxb1 nucleus are more likely responsible for the effects induced by the lesions.

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**POSTER 19**

## Role of the opioidergic receptors on the motor activity and dyskinesia in 6-OHDA parkinsonian rats

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Locomotor disorders like bradykinesia or hesitation of gait initiation are a hallmark of Parkinson's disease (PD). Levodopa (L-DOPA) remains the most effective treatment of PD symptoms although chronic L-DOPA treatment is responsible for the development of motor fluctuations ("ON/OFF" phenomena) and dyskinesia (called "abnormal involuntary movements" AIMs in animals). Opioidergic transmission is involved in basal ganglia function and is mediated through several opioid receptors (μ, δ, κ) and the striatal endogenous peptides enkephalin (ENK) and dynorphin (DYN). Changes in ENK and DYN expression have been described in both untreated and treated PD animals but the function of the striatal opiodergic system in PD is largely unknown.
Here, we hypothesized that an increase of the expression of opioid receptors is linked with secondary compensatory mechanisms leading to both an increase in the spontaneous motor behavior and to the development of dyskinesia in PD rats under L-DOPA treatment. The purpose of this study was thus to investigate whether the opioid receptors expression is correlated with the locomotor activity and the severity of dyskinetic movements, and second to investigate whether the locomotor activity is correlated with the severity of dyskinetic movements.
We used three parkinsonian animals groups treated with chronic injections of L-DOPA 8 mg/kg, 6 mg/kg and Saline, respectively and one group of "Naive" (not lesioned) animals receiving L-DOPA 8 mg/kg. The motor activity of all groups was evaluated by an "Open Field test" at several phases of L-DOPA treatment. The rats were also rated for dyskinetic AIMs. We performed immunohistochemical analysis for the anti- μ and anti- δ opioid receptors in all PD rats.
The behavioral findings showed that PD rats always increased their locomotor activity in response to L-DOPA. However, the motor activity was not linked with the severity of dyskinetic movements. Only the rotational AIMs were correlated with an increased motor activity during chronic L-DOPA treatment. The immunohistochemical analysis showed a higher localization of μ receptors in the striosomes of striatum, compared to an homogeneous distribution of δ receptors in the matrix. All PD rats showed a reduction of μ opioid receptors optical density in the striosomes of the lesioned striatum, compared to the not lesioned side. The expression of μ receptors was correlated to the motor responses and no correlation was found with the dyskinetic movements.
We conclude that opioid receptors are differently involved in the spontaneous motor responses and the appearance of dyskinetic movements in PD rats under L-DOPA treatment.

**POSTER 20**

**Notch/RBPJκ Mediated Activation of pAkt Signaling Pathway Following Seizures Results in Neurodegeneration via Erroneous Cell-Cycle Re-entry.**

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Neuronal demise is a principal cause of irreversible behavioral impairments associated with several neurodegenerative disorders. Although these disorders do not necessarily share the same pathophysiology, they all ultimately result in neurodegeneration in specific neuronal circuits. Hence, it is tempting to speculate that various neurodegenerative disorders may finally impinge upon common molecular pathways that result in neurodegeneration.

Our group previously showed that Notch signaling is aberrantly induced in the mouse model of stroke and likely contributes to cell death. We have found that kainate-induced excitotoxicity causes S-phase reentry in hippocampal CA-field neurons, which also show nuclear expression of Notch-1. Furthermore, kainate-induced excitotoxicity is associated with a concomitant Notch-dependent phosphorylation of AKT and its substrate GSK3. The phosphorylation-induced inactivation of GSK3 is associated with decreased phosphorylation of CyclinD1. This results in cell cycle reentry through the activation of CyclinD-Rb-E2F1 axis. RBP-J□ conditional knockout (RBPJKcKO) mice, which lack canonical Notch signaling, show marked resistance to neurodegeneration following kainate-induced excitotoxicity. We also find that pharmacological blockade of both pAKT as well as CyclinD1 activity in wild type mice confers resistance against KA induced neurotoxicity. Thus, we postulate that excitotoxicity causes neurodegeneration by aberrant cell cycle initiation through pAkt signaling pathway in a Notch-dependent manner. Indeed, studies on postmortem specimens from patients with Alzheimer's disease have shown upregulation of Notch1 as well as increase in phosphorylation of Akt and Gsk3, along with the upregulation of cell cycle related genes in degenerating neurons.

These studies will help us unravel the unique mechanisms of neuronal death involving cell cycle re-entry and pave a way to identify common therapeutic targets to prevent neurodegeneration and associated behavioral alterations.

**POSTER 21**

**Cocaine-evoked plasticity at susceptible accumbal synapses controls relapse**

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Relapse is a frustrating, yet frequent feature of addiction. Addictive drugs like cocaine evoke synaptic plasticity in the nucleus accumbens (NAc) that may underlie such pathological behavior. However, the identity of connections affected and proof of causality remain to be established. Here, in a murine model of delayed relapse, we show that medial prefrontal cortex (mPFC) or ventral hippocampus (vHippo) inputs onto D1-receptor-medium spiny neurons (D1R-MSNs) express contrasting forms of drug-evoked synaptic plasticity. Cocaine seeking correlates with rectifying AMPA receptor transmission and reduced AMPA/NMDA ratio at mPFC to D1R-MSN synapses. In contrast, at vHippo to D1R-MSN synapses the AMPA/NMDA ratio is increased. Optogenetic restoration of synaptic transmission *in vivo* in both afferents abolishes cue-induced seeking while reversal at vHippo synapses alone has no effect. Thus, we identify "susceptible synapses" in the NAc through which cocaine alters accumbal integration to cause relapse. Our findings may inspire novel approaches to drug-addiction and other synaptic diseases.

**POSTER 22**

## Neuroepithelial cell to neuroblast transition in the developing *Drosophila* optic lobe

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During brain formation the path from neural stem cells to differentiated neurons is a step-wise process with many intermediate cellular states. The correct spatiotemporal regulation of this process ensures proper neuronal identity and connectivity.

In order to identify conserved mechanisms underlying neural stem cell proliferation and neuronal differentiation we are studying neurogenesis in the *Drosophila* visual system. In the developing optic lobe, neuroepithelial cells divide symmetrically to extend the pool of stem cells before switching to asymmetrically dividing neuroblasts. This transition is regulated by a proneural wave that sweeps across the neuroepithelium and transiently downregulates Notch signaling activity.

The transcription factor Tailless (Tll) reveals high expression in the lateral neuroepithelium and its expression decreases towards the neuroepithelial to neuroblasts transition zone. We find that a 1.5kb *tll* enhancer fragment can drive restricted expression in the optic lobe. A tightly regulated expression level of Tll is crucial for normal neuroepithelial morphology. Both knockdown of *tll* expression and *tll* misexpression targeted to the entire neuroepithelium leads to laterally extended neuroepithelias with abnormal morphology. Clonal loss- and gain-of *tll* function leads to apical constrictions of epithelial cells and extrusion. In addition *tll* misexpression clones result in reduced Notch activity in a cell-autonomous as well as a non-autonomous manner.

In our working model Tll interacts with Notch signaling to regulate the neuroepithelial to neuroblast transition in the optic lobe. This work is of great interest to gain insight in the role of the Tll mammalian homologue Tlx that has also been implicated in regulating neural stem cell maintenance and differentiation.

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