UNIVERSITÄT OSNABRÜCK

3. Westerberger Herbsttagung

Perspektiven der molekularen Neurobiologie

Cell and Brain Imaging

Plus: A Neurobiological View of Plants - Grey, White and Green Matter

Friday, September 22nd, 2006, 09:00 am
Neurobiology / Neurobiopsychology, Barbarastr. 11, Main Lecture Hall

Cell Imaging:

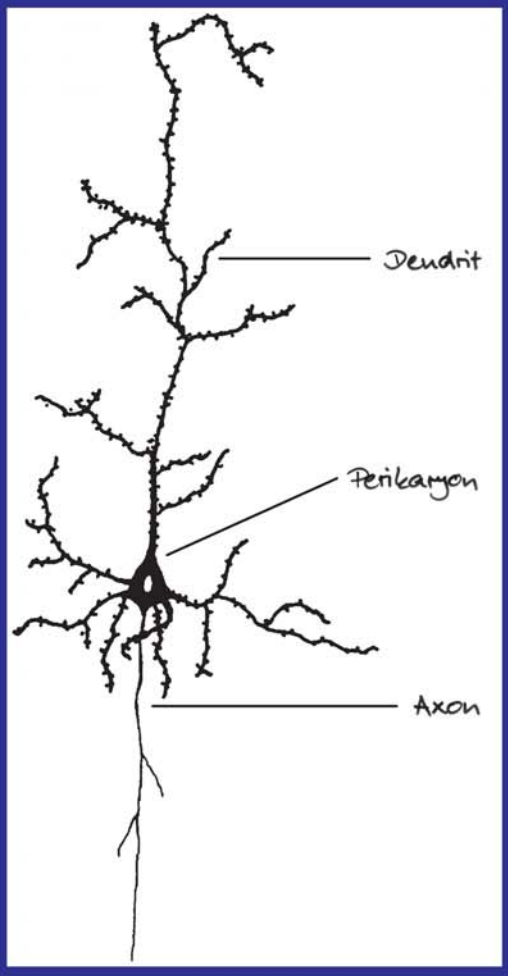
C. Duch
(Arizona State University, Phoenix, Arizona)

T. Mrsic-Flögel
(MPI für Neurobiologie, Martinsried)

J. Kerr
(MPI für Medizinische Forschung, Heidelberg)

C. Weissmann
(Neurobiologie, Osnabrück)

C. Tackenberg
(Neurobiologie, Osnabrück)



Brain Imaging:

C. Moll
(Uniklinikum HH-Eppendorf, Hamburg)

L. Muckli
(MPI für Hirnforschung, Frankfurt/Main)

D. Weiller
(Neurobiopsychologie, Osnabrück)

Plants:

F. Baluska
(Universität Bonn)

unterstützt durch die Deutsche Forschungsgemeinschaft (Graduiertenkolleg "Molekulare Physiologie: Wechselwirkungen zwischen zellulären Nanostrukturen" und Sonderforschungsbereich "Membranproteine: Funktionelle Dynamik und Kopplung an Reaktionsketten) sowie die Nikon GmbH (Düsseldorf)

Kontakt: brandt@biologie.uni-osnabrueck.de - Organisationskommittee: Roland Brandt, Adnan Ghori, Angelika Hilderink, Monika Hundelt, Gunnar Jeserich, Peter König, Christian Rickert, Christian Tackenberg, Carina Weissmann, Daniel Weiller

3rd Westerberger Herbsttagung
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Friday, September 22, 2006, 9:00 a.m.
Faculty of Biology and Chemistry, Barbarastr. 11, Main Lecture Hall

Program

9:00 Introduction (Roland Brandt and Peter König, Osnabrück)

Session I: Cell Imaging (Chair: R. Brandt)

9:15 Lecture 1: Thomas Mrsic-Flögel (MPI für Neurobiologie, Martinsried):
"Imaging plasticity in mouse visual cortex"

10:00 Lecture 2: Jason Kerr (MPI für Medizinische Forschung, Heidelberg):
"Combining two-photon imaging with electrophysiology in vivo: from the single cell to the network"

10:45 - Coffee Break -

11:15 Progress Talk 1: Rafael Kurtz (Neurobiologie, Universität Bielefeld):
"Adaptation in fly visual motion-sensitive neurons"

11:45 Progress Talk 2: Carina Weissmann (Neurobiologie, Osnabrück):
"Tau on the move: Photoactivation to study protein dynamics in living cells"

12:15 Progress Talk 3: Christian Tackenberg (Neurobiologie, Osnabrück)
"Effects of Alzheimer's disease relevant modifications of tau and APP on neurodegeneration and synaptic plasticity in an ex vivo model of the hippocampus"

13:00 - Lunch break (Buffet) and Poster session (part I) -

Special Lecture (Chair: M. Hundelt)

14:00 Dr. František Baluška (Universität Bonn): "A *neurobiological view of plants*"

Session II: Brain Imaging (Chair: P König)

14:45 Lecture 3: Christian Moll (Universitätsklinikum Hamburg-Eppendorf, Hamburg):
"Listening to single cells of the human thalamus and basal ganglia"

15:30 Lecture 4: Lars Muckli (Max-Planck-Institut für Hirnforschung, Frankfurt):
"Mind the gap – cortical activity in response to apparent motion and motion imagery"

16:15 Progress Talk 4: Daniel Weiller (Neurobiopsychologie, Osnabrück):
"Navigation in an artificial agent"

16:45 Concluding remarks: R. Brandt and P. König

17:00 - Coffee and Poster session (part II) -

18:00 End of Meeting

Organizational Committee:
Roland Brandt, Adnan Ghori, Angelika Hilderink, Monika Hundelt, Gunnar Jeserich, Peter König, Christian Rickert, Christian Tackenberg, Carina Weissmann, Daniel Weiller

Supported by the DFG (GRK 612 and SFB 431) and Nikon GmbH
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Introduction

The symposia on „Perspectives of Molecular Neurobiology“ (or in German: „Westerberger Herbsttagung zu den Perspektiven der molekularen Neurobiologie“) have been started on the occasion of the foundation of the Department of Neurobiology in Osnabrück in 2002 and have already established a little tradition at this University. The symposia take place in a biyearly manner and every symposium is focused on a topical issue (booklets of the last two symposia are available on the homepage of the Department at „archives“).

We decided to focus this year’s symposium on the topic „Cell and Brain Imaging“ and organized it as a joint symposium with the Department of Neurobiopsychology of the Cognitive Science Institute. Collaborations across disciplines are a characteristic feature at the University of Osnabrück. An exciting example of an interdisciplinary approach provides the use of modern imaging techniques which involves and addresses important questions in physics, biology, psychology and medicine. In addition, even from a neuroscience view-point, this meeting is very interdisciplinary as you can see from the subtitle „Grey, White and Green Matter“ - a special lecture will be given on a „Neurobiological View of Plants“.

In the morning session of this symposium several speakers will give an overview about different aspects of „cell imaging“ and will present latest results in their research. Unfortunately, Dr. Carsten Duch from the Arizona State University had to cancel due to an accident of a family member. On behalf of the organizers, I want to wish him and his family all the best. Fortunately, Dr. Rafael Kurtz from the Department of Neurobiology at the University of Bielefeld agreed to contribute a lecture despite rather short notice so that invertebrate systems remain to be covered in this meeting. After lunch we will continue with a special and perhaps controversial lecture on „Plant Neurobiology“. In the afternoon session, brain imaging approaches will be in the center of interest. With this symposium we aim to present an update about the current status and the power of different imaging techniques and about key questions that can be approached in the future.

In addition to the main lectures which are given by speakers from Munich, Heidelberg, Bielefeld, Bonn, Hamburg and Frankfurt, several members of the organizing Departments „Neurobiology“ and „Neurobiopsychology“ will give short „progress reports“. These progress reports should give you a flavor about local research activities and how our work relates to the research program of the „Neuroscience community“.

The lectures and progress talks at the symposium are flanked by a poster session and a microscope presentation of Nikon GmbH. A collection of the „abstracts“ of the lectures, the progress talks and the posters are included in this booklet.

I would like to thank the co-organizers of this meeting Adnan Ghori, Angelika Hilderink, Monika Hundelt, Gunnar Jeserich, Peter König, Christian Rickert, Christian Tackenberg, Carina Weissmann und Daniel Weiller. Dr. Monika Hundelt will be the chairperson of the special lecture and Prof. Peter König chairperson of the afternoon session. I also thank all members of the Departments for their help in preparing coffee, booking hotels, choosing the buffet, taking photographs, organizing the poster boards etc. In addition I would like to thank the local „Sonderforschungsbereich 431“, the local „Graduate College“ and Nikon GmbH (Düsseldorf) for financial support. Of course, as every time, a special thanks goes to all speakers for coming here and for contributing to an exciting meeting on „Cell and Brain Imaging“.

R. Brandt (Head of the Department of Neurobiology)

3rd Westerberger Herbsttagung
CELL AND BRAIN IMAGING
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List of Abstracts

Abstract #01: "Imaging plasticity in mouse visual cortex", Thomas Mrsic-Flogel (MPI für Neurobiologie, Martinsried)

Abstract #02: "Combining two-photon imaging with electrophysiology *in vivo*: from the single cell to the network", Jason N. D. Kerr (Max Planck Institute for Medical Research, Heidelberg)

Abstract #03: "Adaptation in fly visual motion-sensitive neurons is activity-regulated but probably independent from calcium", Rafael Kurtz (Neurobiologie, Universität Bielefeld)

Abstract #04: "Tau on the move: Photoactivatable molecules to study protein dynamics in living cells", C. Weissmann[#1], H.J. Reyher[#2], H.J. Steinhoff[#2], R. Brandt[#1] (Dept. of Neurobiology[#1] and Experimental Physics[#2], University of Osnabrück)

Abstract #05: "Effects of Alzheimer's disease relevant modifications of tau and APP on neurodegeneration and synaptic plasticity in an *ex vivo* model of the hippocampus", Christian Tackenberg (Dept. of Neurobiology, University of Osnabrück)

Abstract #06: "Plant Neurobiology: A neurobiological view of plants", František Baluška (University of Bonn)

Abstract #07: "Listening to single cells of the human thalamus and basal ganglia", Christian K.E. Moll, Andreas K. Engel & the Interdisciplinary Functional Neurosurgery Group (University Medical Center Hamburg-Eppendorf)

Abstract #08: "Mind the gap – cortical activity in response to apparent motion and motion imagery", Lars Muckli (Max Planck Institute for Brain Research, Frankfurt am Main)

Abstract #09: "Navigation in an artificial agent", Daniel Weiller (Dept. of Neurobiopsychology, Universität Osnabrück)

Abstract #10: "Form and function of individual neurons", Carsten Duch (Arizona State University)

Abstract #11: "Effects of the cholinergic agonist nicotine on reorienting of visual spatial attention and top down attentional control", Christiane M. Thiel[1,2], Gereon R. Fink[2,3] ([1] Cognitive Neurobiology, Institute of Biology and Environmental Sciences, University of Oldenburg, [2]Department of Medicine, Institute of Neuroscience and Biophysics, Research Centre Jülich; [3] Department of Neurology, University Hospital, Cologne University)

Abstract #12: "fMRI data predict individual differences of behavioral effects of nicotine: A partial least square analysis", Carsten Giessing[a,b,c], Gereon R. Fink[a,b,d], Frank Rösler[e], Christiane M. Thiel[a,b,c] ([a]Institute of Medicine, Research Centre Jülich; [b]Brain Imaging Centre West, Research Centre Jülich, [c]Cognitive Neurobiology, Institute of Biology and Environmental Sciences, University of Oldenburg, [d]Department of Neurology, University Hospital, Cologne University; [e]Department of Psychology, Philipps-University, 35032 Marburg, Germany)

Abstract #13: "Pseudohyperphosphorylation of tau is sufficient to induce aberrant sprouting and activation of ERK1/2 in transgenic mice", Hundelt, M.[1], Selle, K.[1], Kosfeld, A.[1], Fath, T.[2], Schultz, C.[3], Götz, J.[4], von Engelhardt, J.[5], Monyer, H.[5], and Brandt, R.[1] ([1]Department of Neurobiology, University of Osnabrück, Germany, [2]The Children's Hospital at Westmead, Australia, [3]Dr. Senckenbergische Anatomy, University of Frankfurt/Main, Germany, [4]Brain and Mind Research Institute, University of Sydney, Australia, [5]Department of Neurobiology, University of Heidelberg, Germany)

Abstract #01:

Imaging plasticity in mouse visual cortex

Thomas Mrsic-Flogel
MPI für Neurobiologie, Martinsried

The brain has a remarkable ability to adapt to changes in the sensory environment. We are interested in understanding the mechanisms by which neurons in the cerebral cortex adapt to sensory experiences during development as well as later in life. Specifically, we manipulate the visual environment of mice to examine the effect this has on the function and structure of neuronal circuits in the visual cortex. Following a brief period of eyelid closure, neurons in binocular cortex shift their relative responsiveness to stimulation of the two eyes in favor of the eye that had remained open during the deprivation procedure. We use different imaging methods to asses the effect of this plasticity paradigm on the spatial representation and magnitude of eye-specific neuronal responses. Intrinsic-signal imaging, which measures the integrated activity of thousands of neurons, enables us to map and quantify the representations of the two eyes in the visual cortex in normal and deprived animals. To investigate the effects at the single cell level, we use two-photon calcium imaging in vivo, a method that enables simultaneous visualization of the activity from hundreds of individual neurons. Finally, at the level of individual synapses, we use two-photon imaging to monitor the dynamics of synaptic structures in GFP-labeled neurons in the same animal over weeks. Together, these approaches enable us to describe how plasticity is expressed at different stages of neuronal processing hierarchy in the visual cortex in response to altered sensory experience.

Abstract #02:

Combining two-photon imaging with electrophysiology *in vivo*: from the single cell to the network

Jason N. D. Kerr
Dept. Cell Physiology & Dept. Biomedical Optics, Max Planck Institute for Medical Research, Heidelberg, Germany.

Understanding how information is represented and processed in the mammalian neocortex requires measurement of spatiotemporal activity patterns in identified networks of neurons *in vivo*. What will be required is the ability to be simultaneously record both input and output of cortical microcircuits with single-cell and single-spike resolution. Recently, two-photon laser scanning microscopy (2PLSM) has provided a viewing window into the *in vivo* brain. The advantages of multi-photon laser excitation combined with *in vivo* bulk labeling techniques have been exploited to image both subcellular and cellular structures within the mammalian brain, on time scales ranging from milliseconds to weeks. Bulk loading of brain tissue with Acetoxymethyl (AM) ester derivatives of calcium indicators has become a potentially powerful tool in the quest to understand encoding of information in neuronal populations. Several issues arise with the use of this technique: 1) all tissue and structures are labeled with these dyes requiring specific counterstaining with either genetically encoded labels or additional dyes such as astrocyte specific sulforhodamine 101. 2) because of sparse neuronal action-potential (AP) firing in many cortical areas, it is therefore necessary to ensure the detection of single AP evoked calcium signals. In addition, there is a compromise between the spatial/temporal resolution and signal to noise ratio of signal detection. Combining these imaging techniques with simultaneous targeted electrophysiological recordings allows for the probing of neuronal circuits as well as the calibration of neuronal electrical signals with imaging data. Here I will present work that combines both 2PLSM imaging of on-going neuronal population activity and various electrophysiological techniques to simultaneously record neuronal activity during sensory stimulation with single cell and single AP resolution. Using these techniques we addressed how sparse firing manifests to encode sensory input and how variable the responses are on a single trial basis. Results revealed that the spatial relationship of layer 2/3 neurons to the underlying layer IV anatomy dictated the spontaneous activity as well as the response fidelity to sensory input. In addition, we found that patterns of activity evoked from single stimulations were more variable than activity patterns in spontaneous controls. Overall, whisker deflection created stronger pairwise correlations within the network that were not present in spontaneous activity. We conclude that although single layer 2/3 somatosensory neurons display sparse action potential firing in response to sensory input, many features of the stimulation are available at the population level on a single trial basis.

Abstract #03:

Adaptation in fly visual motion-sensitive neurons is activity-regulated but probably independent from Calcium

Rafael Kurtz
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Motion-sensitive neurons in the blowfly brain present an ideal model system for the study of adaptation and its functional significance in a behavioural context. Several different adaptation phenomena have been described, but as yet it is largely unknown which of these effects are based on physiological processes in the motion-sensitive neurons themselves and which originate in previous processing stages [1-3]. One form of adaptation is specifically generated during motion in the preferred-direction and is associated with a prominent after-hyperpolarization (AHP) following cessation of stimulus motion [2;3]. The AHP is accompanied by a decrease in neuronal input resistance. This suggests that direction-selective adaptation is generated in the motion-sensitive neurons themselves by the opening of activity-dependent ion channels. Ca^{2+}-dependent ion channels have previously been proposed to underlie direction-selective adaptation, because the AHP and dendritic Ca^{2+} accumulation are correlated in their strength and timecourse [3]. To test the involvement of Ca^{2+} in adaptation directly, I artificially elevated the cytosolic Ca^{2+} concentration in single neurons by UV photolysis of caged Ca^{2+}. As monitored by Ca^{2+} imaging, this procedure leads to high elevations of the cytosolic Ca^{2+} concentration, equal to those after several seconds of stimulation with preferred-direction motion. However, artificial Ca^{2+} elevations in the absence of visual motion did neither elicit an AHP nor a conductance change. This result renders an involvement of Ca^{2+} in the intrinsic regulation of direction-selective adaptation improbable.

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[2] Harris,R.A., O'Carroll,D.C., Laughlin,S.B., Contrast gain reduction in fly motion adaptation, Neuron, 28 (2000) 595-606.

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Abstract #04:

Tau on the move: Photoactivatable molecules to study protein dynamics in living cells

C. Weissmann[#1], H.J. Reyher[#2], H.J. Steinhoff[#2], R. Brandt[#1]
Dept. Of Neurobiology[#1] and Experimental Physics[#2], University of Osnabrück

With the discovery of fluorescent proteins like GFP, the presence and distribution of different proteins within cells has been easily visualized by expressing the fluorescent molecules fused to the protein of interest. Different techniques like photobleaching and fluorescence recovery after photobleaching (FRAP) have made it possible to go further on the analysis of how cell components move and interact with one another[1]. The upcoming of new tags have increased the type of information obtained from studying proteins in living cells.
The mutations of GFP to obtain the PA-GFP (Photoactivatable GFP)[2] molecule allows to study a subpopulation of photoactivated molecules without the need of the high energy used in FRAP experiments and disregarding any newly synthesized molecule throughout the experiment.
To our knowledge, PA-GFP molecules have been used, so far, mainly to study movement of intracellular components in a qualitative manner[3]and to confirm FRAP experiments.
Here, we describe a system that permits the analysis of the dynamic properties of a cytoskeletal protein in living cells and yields a quantitative parameter to characterize it.
PC12 cells were used as a neuronal cell model to study different tau proteins fused to PA-GFP. PA-GFP-tau proteins were stably transfected in PC12 cells and clone lines isolated. For the analysis, cells were differentiated with NGF to focus on the behaviour of the proteins within cell processes.
Living cells were imaged with a laser scanning confocal microscope equipped with an incubation chamber and a set of lasers. After activation of a ~7-8um region in cell processes with a 405nm laser, images were acquired at a 1-second interval with a 488nm laser. The pixel analysis of the movies was performed with Matlab program to visualize the movement of the signal within the cell throughout time and determine the fraction of protein present over time at the activated spot.
The analysis yielded differences in the mobility of the proteins investigated. Moreover, the system allows studying the behaviour of the PAGFP-tau protein in the presence of other simultaneously expressed proteins in the cell. Furthermore, the use of drugs that disrupts certain cell components permits the analysis of how the mobility of the protein responds to the varying environment.
The method is of relevance in the study of tauopathies like Alzheimer's disease, that display a different localization of tau proteins, ie. a somatodendritic distribution as compared to the normal axonal distribution. The results obtained so far on PAGFP-tau proteins could give a tentative explanation on how this distribution is achieved in the disease.

[1] Lippincott-Schwartz, Molecular Cell Biology, Nature Reviews, Vol 2, 2001.
[2] Patterson et al, A Photoactivatable GFP for Selective labelling of Proteins and cells, Science, Vol 297, 2002.
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Abstract #05:

Effects of Alzheimer's disease relevant modifications of tau and APP on neurodegeneration and synaptic plasticity in an *ex vivo* model of the hippocampus

Christian Tackenberg
Dept. of Neurobiology, University of Osnabrück

Alzheimer's disease (AD) is the most common neurodegenerative disorder. AD is characterized by loss of neurons, alterations in synaptic integrity and by two types of protein aggregates in the brain, namely amyloid-plaques and neurofibrillary tangles (NFTs). Amyloid plaques consist of aggregated Aß, a fragment of the Amyloid Precursor Protein (APP). NFTs contain hyperphosphorylated tau protein as their major component.
To determine a potential role of hyperphosphorylated tau in AD pathology, we constructed a pseudohyperphosphorylated (PHP) tau, which mimics key structural and functional aspects of AD-like hyperphosphorylated tau protein (Eidenmüller *et al.,* 2000). Enhanced green fluorescent protein (EGFP) tagged tau constructs were cloned into the Sindbis virus expression system (Ehrengruber *et al., 1999*) to allow efficient expression in neurons.
The hippocampus is one of the brain regions, which are altered during AD. To analyze a potential role of modified tau during AD, organotypic hippocampal slices were prepared (Stoppini *et al., 1991*) and infected with the Sindbis Virus constructs. High EGFP-tau expression was observed in neurons as early as 7 hours post infection and persisted until 6 days.
To analyze a potential effect of APP or Aß on neurons expressing different tau constructs, hippocampal slices were prepared from APP_{SDL} transgenic C57BL6 mice. These mice express equimolar amounts of $Aß_{1-40}$ and $Aß_{1-42}$ in embryonic age (Leschik *et al., in revision*).
A potential neurodegenerative effect of different tau constructs and/or APP_{SDL}, as well as the influence of APP_{SDL} on synaptic integrity of hippocampal neurons will be analyzed.
Hippocampal *ex vivo* models from transgenic mice in combination with virus-mediated targeted expression of disease relevant tau constructs provide an effective tool to get insights into the molecular pathology of Alzheimer's disease and other neurodegerative disorders.
Aim of this presentation is to introduce techniques of low-resolution live-imaging of infected hippocampal neurons and high-resolution imaging of dendritic spines in combination with algorithm-based automated analysis of spine-density and morphology (Shahani *et al.,* 2006).

Further Reading:
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Shahani, N., Subramaniam, S., Wolf, T., Tackenberg, C., Brandt, R. (2006) Tau aggregation and progressive neuronal degeneration in the absence of changes in spine density and morphology after targeted expression of Alzheimer's disease relevant tau constructs in organotypic hippocampal slices. *J. Neurosci.* 26(22): 6103-6114
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Abstract #06:

Plant Neurobiology: A Neurobiological View of Plants

František Baluška

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Human perception of the outside world relies on so-called 'neural code' which links together sensory signals and neural responses. Similarly in plants, numerous parameters of the physical environment, especially light and gravity, are continuously monitored. Specialized cells are evolutionarily optimised to translate sensory information obtained from this environment into motoric responses. Moreover, physical forces, influences, and insults, all induce immediate electrical responses in plants.

Recent advances in plant cell biology, molecular biology, and ecology have accumulated a critical mass of data which are not 'digestible' within the framework of these classical, disciplines of plant sciences. New approaches are required, and these should be characterized by system-like analysis of information acquisition, storage, processing, and the making of decisions. Plants retrieve from the abiotic environment information critical for their survival, especially relating to light and gravity. Intriguingly, the translation of these physical forces into plant activities – typically differential growth responses – is based on the transcellular transport of auxin, which help to bring about the final shape of the plant body. Thus, this information-bearing molecule is central to our call for plant neurobiology. Recent advances indicate that auxin is secreted out of cells and induces electric responses in adjacent cells. This implicates that auxin, besides being a plant hormone and morphogen, acts also as plant-specific neurotransmitter.

A newly focused field of research in plant biology, called plant neurobiology, is aimed at understanding how plants process information they obtain from their environment in order to develop, prosper and reproduce optimally. The behaviour plants exhibit is coordinated across the whole organism by some form of integrated signaling, communication and response system. This system includes long-distance electrical signals, vesicle-mediated transport of auxin in specialized vascular tissues, and production of chemicals known to be neuronal in animals. Plant neurobiology will be directed toward discovering the mechanisms of signalling in whole plants, as well as among plants and their neighbours.

Literature

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Baluška F, Hlavacka A, Mancuso S, Volkmann D, Barlow PW (2005) Neurobiological view of plants and their body plan. In *Communication in Plants: Neuronal Aspects of Plant Life*, F Baluška, S Mancuso, D Volkmann (eds), Springer-Verlag

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Abstract #07:

Listening to single cells of the human thalamus and basal ganglia

Christian K.E. Moll, Andreas K. Engel

& the Interdisciplinary Functional Neurosurgery Group, Center of Experimental Medicine, Department of Neurophysiology and Pathophysiology, University Medical Center Hamburg-Eppendorf

In the context of contemporary neurosurgery for movement disorders (Parkinson´s disease, dystonia or tremor), therapeutic electrodes are implanted in deep brain structures for chronic electrical stimulation. Intraoperative microelectrode-recordings (iMER) are a valuable tool to guide the neurosurgeon to the subcortical target area with high precision. The characteristic activity of single thalamic and basal gangliar neurons enables the physiologist to delineate nuclear boundaries, to determine functional subdivisions in a nucleus and to localize regions that display pathological firing patterns. Besides their practical relevance, iMER allow unique close-up views of neural processes in human depth structures that may provide novel insights into the pathophysiology of movement disorders. Whereas traditional box-and-arrow-models of basal ganglia function explain symptoms of movement disorders by firing-rate changes, recent pathophysiological ideas stress the importance of the temporal patterning of activity in the basal ganglia circuitry. However, these hypotheses are mainly derived from animal models of movement disorders, which do not accurately reproduce the symptoms of the human disease. The talk will show how pathophysiological ideas from the laboratory can directly be tested in patients using iMER and subsequent local field potential (LFP) recordings from the therapeutic electrode. Recent insights from studies of oscillatory activity in the motor system are highlighted and the implications for basal ganglia function are discussed. Furthermore, we present new data on the electrophysiological correlates of selective attention in thalamus and basal ganglia. We simultaneously recorded EEG, depth LFP and single cell activity from thalamus, subthalamic nucleus and substantia nigra while awake patients carried out a task that provides a comparison between environmental stimuli requiring attention and those that do not. We found attention specific responses in both single cells and LFPs of the human thalamus and basal ganglia that precede the cortical respones. Our findings suggest that different subcortical nuclei are involved in the early processing of salient environmental stimuli.

Abstract #08:

Mind the gap – cortical activity in response to apparent motion and motion imagery

Dr. Dipl.-Psych. Lars Muckli
Max Planck Institute for Brain Research, Frankfurt am Main

We have used various brain imaging techniques (fMRI, EEG, TMS) to study how visual motion illusions and motion imagery are constructed in the visual system of humans. The illusions of apparent motion and apparent rotation are well suited for studying how the visual system constructs and represents spatial relations. Apparent motion induces the impression of a smooth motion in-between two blinking dots. Apparent rotation induces a vivid illusion of apparent motion in three dimensions by presenting two images of an object rotated in space. The functional architecture of early visual areas incorporates analogue representations of the outside world in retinotopic maps. Spatial relations of the outside world are distorted by the cortical magnification but neighbourhood relations are strictly preserved. With the knowledge in mind that stimulus locations activate distinct cortical regions (V1-V3) we can ask whether visual spatial illusions lead to activation at locations corresponding to the filling-in illusion observed in apparent motion and apparent rotation. We have found such illusion related activity in retinotopic visual area V1 only for apparent motion only. In the light of earlier work of our group we proposed that this activity is related to feedback from motion sensitive visual areas V5. The importance of area V5 for motion processing is further highlighted by inactivation studies using TMS. To test the hypothesis of feedback from V5 to V1 we performed EEG experiments that confirmed a sequential order of brain activation from extrastriate to early visual areas. In 3D-apparent rotation and for motion imagery higher visual areas are involved in representing the unseen intermediate illusion related positions and the mental imagery traces.

Abstract #09:

Navigation in an artificial Agent

Daniel Weiller
Neurobiopsychologie, Universität Osnabrück

One of the main problems facing robotics is the implementation of animal-like behaviors, e.g. finding food in known environments. A kind of cell has been found in the brains of mice, which responds as a function of the animal's current location, but invariant of its current viewpoint. These cells are known as "place cells". It is not yet known how these cells contribute to navigation tasks, but their response to spatial position makes them an appealing. We have developed a general system capable of modeling different cognitive processes, which is here used as a "cognitive agent". The agent model is tested by using place cells to solve the task of finding food in a realworld environment.
One of the main aspects of our approach is the definition of "states". The area of the environment, or "field", for which each place cell is active is defined as a place fields. Each point of the environment (in [x,y] co-ordinates) belongs to one of the place fields, and each of these place fields is defined as a state, allowing a transformation into a state space. The agent, controlling the robot, executes different randomlychosen actions on the current state, and in doing so "experiences" the environment.
This experience-collecting behavior is combined with obstacle-avoidance behavior, or "reflexes". Repeating the same action on a state does not necessarily lead to the robot arriving at the same state. Through experience, the agent learns the probabilities of a transition from a certain state to another state with a certain action. In order to find the best path to a present goal – for instance locating food in its environment – the agent uses this experience to choose the action with the highest probability of leading him to the goal, given his current state. By learning the probabilities describing how likely each possible action on a state will result in another experientially connected state, the robot can successfully navigate through its environment.
We compared the mean length of a path taken by the robot to some goal locations with the shortest possible distance that could be taken. The path of the robot was 86% longer than the shortest distance. However, the spatial distribution of the states over the environment accounts for 22% of this difference. The bulk of the remaining 64% deviation from the ideal path length results from the reflex obstacle-avoidance behavior mentioned above. Furthermore, the state transition probabilities cannot be understood only by looking at the relative spatial properties of the states. Looking at the results of different actions performed at single states, we recognized a high correlation between them. Because of the reflexes, the agent cannot control the results of his behavior at the boundaries of the environment – the action it "intended" to execute is not necessarily successful. We introduced a separate component so that the system could account for these uncontrolled behaviors. This can be interpreted as a separate module that contributes to the processing of especially unpredictable and complex situations, like suddenly coming into contact with a wall. With the help of this component the agent can suspend its normal experiencing of the environment for as long as is necessary, thus protecting its learned transition probabilities from the disturbance of such unpredictable events.
Our system uses a bottom-up process to adapt to the environment (learning through experience) and a top-down process to navigate the robot to a goal (using the learned experiences). The definition of an action must not be the same for each state – different states can have different actions. It is easily possible to expand the system by incorporating other actions, i.e. grabbing objects. By using different states and actions within the system, it can easily be expanded to model other cognitive processes.

Abstract #10:

Form and function of individual neurons

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Understanding an adaptive and learning computing system such as the brain requires an understanding of the computations performed by its basic components—individual neurons. At the single neuron level, the means for translating spatio-temporal synaptic input patterns into meaningful output patterns is provided by the geometry of the dendritic tree. To us, geometry includes dendritic shape plus the distribution patterns of synapses, receptors and ion channels within the dendritic tree. Up to date no comprehensive framework exists for translating dendritic morphology and physiology into a functional architecture that can be directly related to behavior.

A fundamental prerequisite for addressing these issues is the ability to relate the structure of individual identified neurons directly to their function, which requires parallel identification of their anatomy, physiology and behavioral function. In holometabolous insects, like *Manduca sexta* and *Drosophila melanogaster,* structure, physiology and function are modified in parallel during metamorphosis, allowing for studies that directly relate dendritic geometry to behavioral function. This postembryonic remodeling has been described in particular detail for the identified motoneurons, MN1-5, which transform from tonically firing larval crawling motoneurons into phasically firing adult flight motoneurons.

We have developed a tool set for semi-automatic geometric reconstruction of neuronal architecture from stacks of confocal images. It provides exact midlines, diameters, surfaces, volumes and branch point locations, and allows analysis of labeled molecule distribution along neuronal surfaces as well as direct export into modeling software. We now combine these novel tools to analyze neuronal geometry in identified insect motoneurons. The genetic power of Drosophila allows expression of fluorescence tagged receptor molecules and membrane channels in selected neurons only, so that their exact locations can be determined in 3-dimensional dendritic tree reconstruction. Dendritic geometry including synapse and channel distribution maps within individual trees is then exported into multi-compartment models to make predictions about their functions for spiking output. These predictions are then tested by genetic manipulations and by behavioral experiments.

This integrative approach now yields novel rules for structure function relationships on the single neuron level; examples are rules such as how excitatory and inhibitory input synapses and specific low voltage activated calcium channels are distributed through entire dendritic trees to mediate behaviorally adequate firing output.

Abstract #11:

Effects of the cholinergic agonist nicotine on reorienting of visual spatial attention and top down attentional control.

Christiane M. Thiel[1,2], Gereon R. Fink[2,3]

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The cholinergic agonist nicotine facilitates reorienting of visual spatial attention in location-cueing paradigms and reduces reorienting-related neural activity in human inferior parietal cortex. Here we use fMRI to explore whether the nicotinic modulation of attentional reorienting is due to a reduced use of top down information provided by the cue. In a within subjects design non-smoking volunteers were given either placebo or nicotine (NICORETTE® 2 mg gum) prior to performing a cued target discrimination task. Attention was either validly (80%) or invalidly (20%) cued to the right or left visual hemifield. The difference in reaction times to invalidly and validly cued targets is termed the 'validity effect' and used as a measure for reorienting. Nicotine reduced the validity effect and reorienting-related activity in right inferior parietal cortex. Further regions consistently modulated by nicotine were the right middle temporal gyrus, the left middle frontal gyrus, the left parahippocampal gyrus and the right cerebellum. Top down modulation of attention directing cues was investigated by comparing occipital activity when attending to the right vs. left visual hemifield. Even though, attention-related modulation of neural activity was present in contralateral fusiform cortex and middle occipital gyrus we found no evidence for differences under placebo and nicotine. Our data supports a role of nicotinic cholinergic receptors in facilitating attentional reorienting via modulation of right inferior parietal, temporal and frontal brain activity. The findings however challenge the view that these effects are due to reduced reliance on top down information.

Abstract #12:

fMRI data predict individual differences of behavioral effects of nicotine: A partial least square analysis

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Reorienting of visuo-spatial attention can be investigated by comparing reaction times to validly and invalidly cued targets ('validity effect'). The cholinergic agonist nicotine reduces the validity effect and neural activity in posterior parietal cortex. Behavioral effects of nicotine in non-smokers are weak and it has been suggested that differences in baseline behavior before nicotine exposure may influence the effect of nicotine. This study investigates whether individual differences in reorienting-related *neural* activity under placebo may be used to predict individual nicotine effects. Individual nicotine effects are defined as the behavioral effects under nicotine that cannot be predicted by the behavioral data under placebo. Fifteen non-smoking subjects were given either placebo or nicotine gum (2 mg) prior to performing a cued target detection task inside an MRI scanner. The results of a partial least square (PLS) analysis suggest that neural data under placebo can be used to predict individual behavioral effects of nicotine. Neural activity in the left posterior cingulate cortex, the right superior parietal cortex, the right dorsal medial prefrontal cortex and the left ventral medial prefrontal cortex significantly contribute to that prediction. We conclude that nicotine effects on reorienting attention depend on individual differences in reorienting-related neural activity under placebo and suggest that fMRI data can contribute to the prediction of individual drug effects.

Abstract #13:

Pseudohyperphosphorylation of tau is sufficient to induce aberrant sprouting and activation of ERK1/2 in transgenic mice

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Hyperphosphorylation of tau is a characteristic of Alzheimer's disease (AD). Our group has established a model for tau hyperphosphorylation by mutating 10 residues from Ser/Thr to Glu to simulate the negative charge of phosphorylated residues ("pseudohyperphosphorylated (PHP)-tau").
In order to analyze temporal and spatial effects of hyperphosphorylation of tau in a systemic context, we have established transgenic mouse lines that express human wild-type (wt)- or PHP-tau under the control of the CamKIIα-promoter that leads to a forebrain specific moderate expression in neurons, i.e. the region where also tau-pathology in AD is abundant.
For the evaluation of tau-induced changes in the transgenic mice, we quantified spine densities in the neocortex and hippocampus of transgenic mice. The spine densitiy was significantly increased in PHP-tau compared to wt-tau expressing mice. It is known that AD is associated with aberrant pre- and postsynaptic sprouting. Axonal sprouting is also observed in transgenic mice expressing mutated amyloid precursor protein (APP) [1], which suggests that Aβ plays a significant role in this process.
We deduce from our results, that (pseudo)-hyperphosphorylation of tau is sufficient to induce aberrant sprouting in the absence of Aβ. Analyses whether this sprouting is induced by pre- or postsynaptic changes and if functionally active synapses are formed are in progress. It will be interesting to determine if stabilization of these newly formed synapses slows or - in contrary - accelerates the progression of the disease.
Sprouting as observed in our PHP-tau expressing mice is part of neuronal differentiation. One family of enzymes that is involved in cell differentiation are mitogen-acitvated protein kinases (MAPK). Western blot analysis was performed with brain lysates from transgenic mice to check whether PHP-tau induced sprouting is associated with MAPK activation. In fact, we also observed an increased activation of the MAPK ERK1/2 evident by phosphorylation of the residues Thr202 and Tyr204.
ERK1/2 is also known to phosphorylate tau at sites characteristic for AD. Our results suggest the presence of a vicious circle by which (pseudo)-hyperphosphorylated tau activates ERK1/2 which in turn phosphorylates tau.

Literature

[1] Phinney, A.L., Deller, T., Stalder, M., Calhoun, M.E., Sommer, B., Staufenbiel, M., and Jucker, M. (1999); J.Neurosci. **19**: 8552-8559.

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Nr. 231/2006
Osnabrück, 2006-09-14

Ins Gehirn geschaut – Neue Methoden in den Neurowissenschaften

Uni Osnabrück lädt zu 3. Westerberger Herbsttagung ein

Das Gehirn birgt noch viele Geheimnisse. Und grundsätzliche Fragen sind noch nicht geklärt: Wie lernen wir? Wie treffen wir unsere Entscheidungen? Wie entstehen neurodegenerative Erkrankungen, wie etwa die Alzheimersche Erkrankung? Und was können wir dagegen tun? Um Einblicke in das Geschehen im Gehirn zu erhalten, werden ständig neue Methoden entwickelt, die es erlauben, einzelne Moleküle, Zellen oder die Aktivitätszustände ganzer Nervenzellverbände sichtbar zu machen. Einige dieser Methoden und die damit gewonnenen Erkenntnisse werden am Freitag, 22. September, auf der 3. Westerberger Herbsttagung vorgestellt. Organisiert wird sie von den Abteilungen Neurobiologie und Neurobiopsychologie der Universität Osnabrück.

Am Vormittag der Tagung stehen Methoden im Mittelpunkt, mit denen einzelne Moleküle in lebenden Zellen und ganze Nervenzellen bis in ihre feinsten Verästelungen sichtbar gemacht werden können. Am Nachmittag wird unter anderem vorgestellt, wie mit Hilfe von Mikroelektroden die Aktivität von Hirnregionen bestimmt werden kann, um beispielsweise Bereiche zu identifizieren, die bei Erkrankungen Fehlfunktionen zeigen. Unter anderem referieren Dr. Carsten Duch (Phoenix, USA), Dr. Thomas Mrsic-Flögel (Martinsried bei München), Dr. Jason Kerr (Heidelberg), Dr. Lars Muckli (Frankfurt) und Christian Moll (Hamburg). Zu der Tagung sind alle Interessierten herzlich eingeladen. Der Beginn ist um 9 Uhr im großen Hörsaal des Biologiegebäudes, Barbarastraße 11. Eine Voranmeldung ist nicht erforderlich.

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Introduction: R. Brandt (Dept. of Neurobiology)
and P. König (Dept. of Neurobiopsychology)

Lecture 1:
T. Mrsic-Flögel, Martinsried

Lecture 2:
J. Kerr, Heidelberg

Progress Talk 2 :
Rafael Kurtz, Bielefeld

Progress Talk 3:
C. Weissmann, Osnabrück

Progress Talk 3 :
C. Tackenberg, Osnabrück

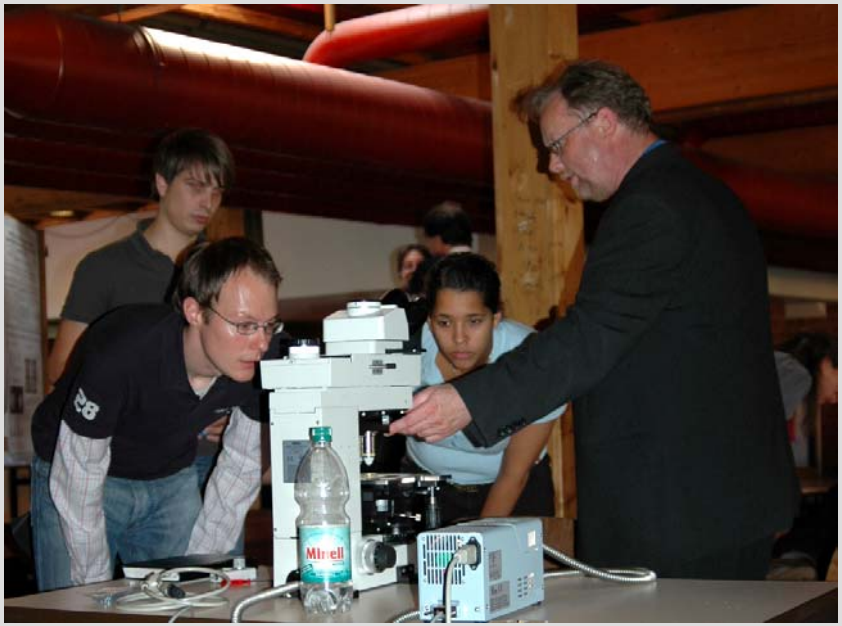
Special Lecture:
F. Baluska, Bonn

Lecture 3:
C. Moll, Hamburg

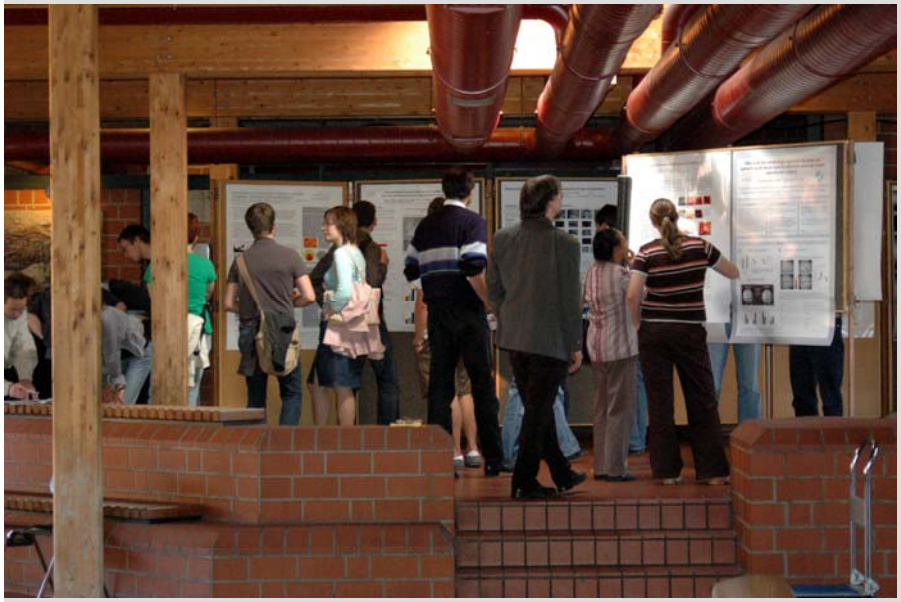
Lecture 4:
L. Muckli, Frankfurt

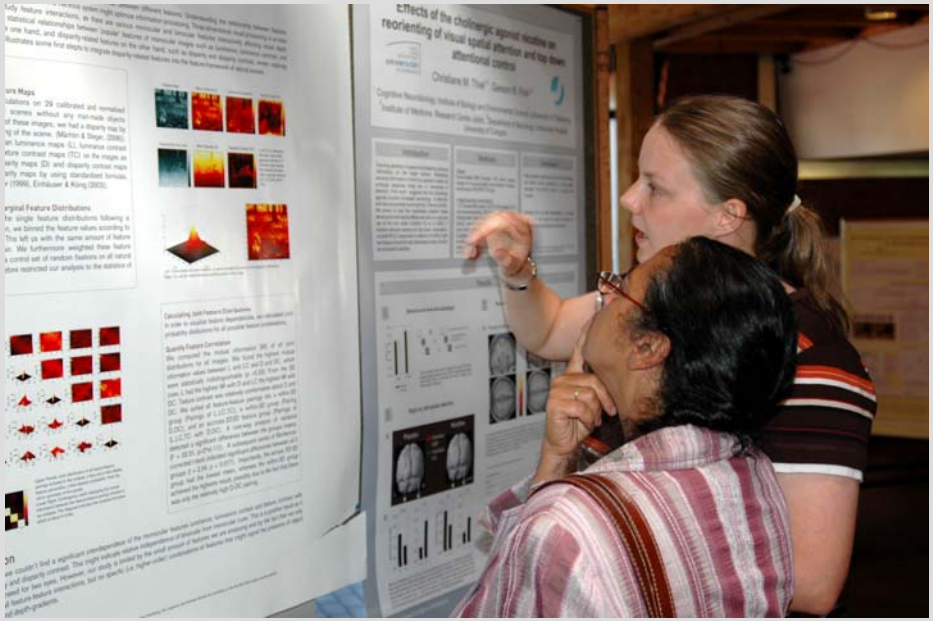
Progress Talk 4:
Daniel Weiller, Osnabrück

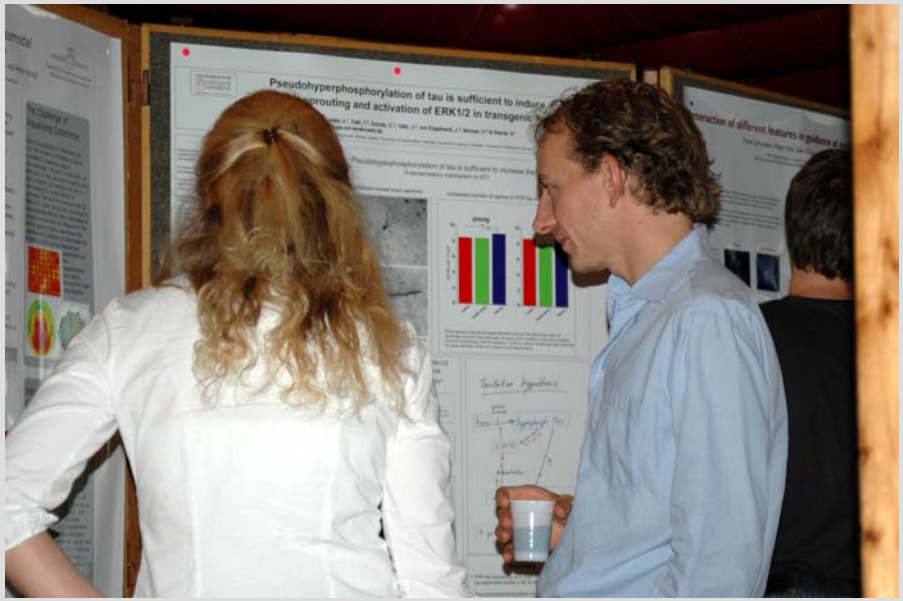
Nikon stand

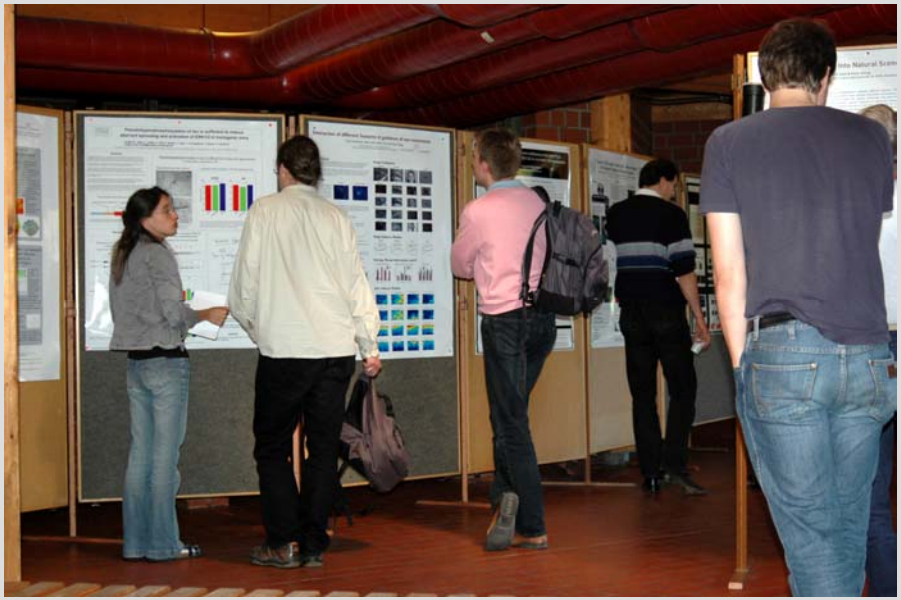


Poster session









Conversations during Coffee and Buffet

Conversations during Coffee and Buffet