7th International Ph.D. Symposium

Berlin Brain Days

2010/*nov.* 1–3

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Max Delbrück Center for Molecular Medicine Berlin-Buch

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Contents

Welcome to the Berlin Brain Days 2010

The Berlin Brain Days are an activity of doctoral students across several independent Berlin institutions. Initiated in 2005 by faculty and students in "Medical Neurosciences" (a graduate school at the Charité), it has subsequently grown year-by-year as the neuroscientific research and training environment has rapidly developed within the city.

The growth in the number and variety of new doctoral programs within Berlin is quite remarkable. In 2005, a research training group of the German Research Council (DFG), on "Learning and Memory" (GRK 1123 – Cellular Mechanisms of Learning and Memory), was established. In 2006, as part of the Excellence Initiative for German universities, the "Berlin School of Mind and Brain" was founded to foster transdisciplinary research at doctoral level across the mind and brain sciences. In 2007, a second and third acquisition of the Excellence Initiative resulted in the establishment of two Clusters of Excellence: "NeuroCure" and "Languages of Emotion", both with additional funding for doctoral students. The doctoral program "Computational Neuroscience" of the Bernstein Center for Computational Neuroscience has now merged with the new DFG research training group "Sensory Computation in Neural Systems". The Helmholtz International Research School "Molecular Neurobiology" has been in existence since 2003.

In December 2008 and 2009, we very successfully joined our forces, and the Berlin Brain Days 2010 again are a common activity of all these programs. Students and faculty alike are highly motivated to learn about the research of neigh-

boring programs, and the Berlin Brain Days have become an important forum for information exchange.

Berlin has a good tradition in fostering activities in the neurosciences: the Berlin Neuroscience Forum has been organized every other year since 1997 and is a common activity of the Berlin universities and Berlin-based collaborative research centers (*Sonderforschungsbereiche*, *Forschergruppen*, *Graduiertenkollegs*, etc.). It regularly attracts 200 neuroscientists to a small resort outside of Berlin, Liebenwalde.

For Berlin Brain Days 2010, we welcome for the second time international guests of the Berlin School of Mind and Brain: the winners of the women's travel awards to young neuroscience, linguistics and philosophy students. We look forward to hearing about their research as they too will attend the symposium and present posters.

It is in our best interest that we join forces, interact closely, and continue to develop Berlin as a hotspot for research across the neurosciences. With this in mind, I am convinced that we will have a very interactive and successful meeting that will result in new collaborations within the Berlin neuroscience research community.

Helmut Kettenmann, Conference Chair

Monday, 1 November 2010
Kaiserin-Friedrich-Stiftung | Robert-Koch-Platz 7 | 10115 Berlin

Opening session

18.00 **Helmut Kettenmann** › Opening address
Dietmar Schmitz › Chair
Edvard I. Moser "Grid cells, place cells and the brain's representation of space"

19.10 **Annette Grüters-Kieslich** (Dean, Charité – Universitätsmedizin Berlin)
Klaus Obermayer (Director Graduate Programs, Bernstein Center for Computational Neuroscience Berlin)
› Award of master's diplomas and doctoral certificates

19.30 **Daniel Schlacks** › Student address

19.45 M. Sc. student representative › Teaching awards

20.00 Reception

Tuesday, 2 November 2010
Max Delbrück Center for Molecular Medicine Berlin-Buch | Conference Center MDC.C, lecture hall "Axon", Robert-Rössle-Straße 10 | 13125 Berlin

Session 1

09.00 **Helmut Kettenmann** › Introduction
David R. Colman "Evolutionary origins and organization of the CNS synapse"

10.00 **Ellen Barker, Nora Mecklenburg, Anna Soriguera Farrés** › Ph. D. talks

Session 2

11.15 **Hauke R. Heekeren** › Introduction
Tor D. Wager "The origins of pain in the central nervous system: Insights from manipulations of expectation and affective value"

12.15 **Ryszard Auksztulewicz, Thorsten Kahnt, Soyoung Q Park** › Ph. D. talks

13.00 Lunch

13.45 Poster presentations (+ coffee) **odd numbers**

Session 3

15.00 **Felix Wichmann** › Introduction
Eero P. Simoncelli "Bayesian modeling of visual motion perception"

16.00 **Jan Clemens, Hannah Dold, Evelin Wacker** › Ph. D. talks

Wednesday, 3 November 2010
Max Delbrück Center for Molecular Medicine Berlin-Buch | Conference Center MDC.C, lecture hall "Axon", Robert-Rössle-Straße 10 | 13125 Berlin

Session 4

09.00 **Uwe Heinemann** › Introduction
Richard Miles "Hippocampal synchrony in disinhibited guinea-pig slices and human epileptic tissue"

10.00 **Anna Maslarova, Etienne Ndzié Atangana, Ranjeet Verma** › Ph. D. talks

10.45 Poster presentations (+ coffee) **even numbers**

12.00 Lunch

Session 5

13.30 **Gudrun Ahnert-Hilger** › Introduction
Lutz Birnbaumer "Signal Transduction by G Proteins: Focus on molecular aspects of activation and deactivation of regulatory GTPases"

14.30 **Jens Baron, Chia-Ling Chang, Agustin Liotta** › Ph. D. talks

15.15 Improv Comedy by Creative Heads (during evaluation for "Best Talk" and "Best Poster")

15.45 Award of "Best Talk" and "Best Poster"

20.00 BBD Party
Sanatorium 23 | Frankfurter Allee 23 | 10247 Berlin
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OPENING LECTURE

Monday, 1 November 2010

18.00 **Edvard I. Moser**
Grid cells, place cells and the brain's representation of space

Opening address **Helmut Kettenmann**
Max Delbrück Center for Molecular Medicine Berlin-Buch

Chair **Dietmar Schmitz**
Charité – Universitätsmedizin Berlin

Edvard I. Moser

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2007–present	Founding Director of Kavli Institute for Systems Neuroscience
2002–present	Founding Director of Centre for the Biology of Memory
1998–present	Professor of Neuroscience
1996–1998	Associate Professor of Biological Psychology
1994–1996	Postdoc, The University of Edinburgh and University College London
1991–1995	Ph.D. student, Oslo University

Edvard I. Moser

Grid cells, place cells and the brain's representation of space

Kavli Institute for Systems Neuroscience, NTNU, Trondheim, Norway

Grid cells are a key component of the brain network for representating self-location in allocentric space. These cells fire selectively at regularly spaced positions in the environment such that, for each cell, activity is observed only when the animal is at places that together define a repeating triangular pattern tiling the entire environment covered by the animal. The scale of the grid map is topographically organized in that the spacing of the grid increases from the dorsal to the ventral end of medial entorhinal cortex. In the first part of the talk, I will show that the organization of the grid map is modular and that HCN channels contribute to the determination of grid scale. I will also show that grid cells co-localize with head-direction cells, conjunctive grid × head direction cells, and border cells, which each contribute to a dynamically updated metric representation of current location in the medial entorhinal cortex. Based on studies using a virus-mediated approach to selectively express photoresponsive channel proteins in entorhinal cells with projections to the hippocampus, I shall present preliminary data suggesting that grid cells, head direction cells and border cells may all provide direct input to place cell maps in the hippocampus.

An important difference between grid cells and place cells is the tendency for place cells to form orthogonal representations in different environments. This orthogonalization process is thought to depend on the formation of attractor states in recurrent neuronal networks. While several experimental observations are consistent with the presence of attractors in the entorhinal cortex and hippocampus, the dynamic processes supporting attractor dynamics, at the time scale of behaviour, are not well understood. I will show that, in response to an instantaneous transition between two familiar and similar spatial contexts, hippocampal CA3 networks undergo short periods of flickering between pre-formed representations before settling in on the representation most consistent with the new cue configuration, several seconds after the cue change. During the flickering period, convergence to each representation may take place within a single theta cycle and fully expressed representations may alternate at theta time-scale frequencies. The data suggest that, in CA3, pattern completion dynamics repeats within each individual theta cycle. The repetition may facilitate error correction, thus enhancing the discriminative power of the system in the presence of conflicting input cues from spatial representations in entorhinal cortex and stored representations within the hippocampus.

SESSION 1

Tuesday, 2 November 2010

09.00 **David R. Colman**
Evolutionary origins and organization of the CNS synapse

10.00 **Ellen Barker**
Nora Mecklenburg
Anna Soriguera Farrés
› Ph. D. talks

Introduction **Helmut Kettenmann**
Max Delbrück Center for Molecular Medicine
Berlin-Buch

Chair **Kristin Stock**
Helmholtz International Research School
Molecular Neurobiology

David R. Colman

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2002–present	Director, Montreal Neurological Institute
1993–2002	Annenberg Professor of Molecular Biology and Neuroscience, Department of Neurology and The Fishberg Research Center for Neurobiology, The Mount Sinai School of Medicine
1987–1993	Associate Professor, Departments of Anatomy and Cell Biology, and Pathology in the Center for Neurobiology and Behavior, College of Physicians and Surgeons of Columbia University
1983–1987	Assistant Professor, Department of Cell Biology, New York University School of Medicine

David R. Colman

Evolutionary origins and organization of the CNS synapse

Montreal Neurological Institute, Montreal, Quebec, Canada

Some of the fundamental subcellular mechanisms that organize the plasma membranes of uniform, simple epithelia are utilized also by neurons. For example, adherens junctions abound on neuronal surfaces; these junctions connect one neuron to another and co-localize with the physiological synapse. The argument has been presented that the adherens junction is the evolutionary antecedent of the chemical synapse. In brief, the evidence for this is that the morphologies of the epithelial adherens junction and the CNS synaptic junctional complex are very similar; both are adhesive and signaling devices consisting of plasma membrane thickenings with underlying electron-dense material. There is a narrow, remarkably uniform cleft between plasma membranes of 150–300 Angstrom units. The junctional membranes are invariantly in register, parallel to one another, and cannot be separated from one another by physical means. Most telling, it is clear that the adhesive mechanisms that form both the adherens junction and the CNS synapse depend on identical adhesive elements, in that both are at least in part cadherin-mediated structures, containing not only the calcium-dependent cadherin adhesion molecules of all epithelia, but also the cadherin binding proteins as well. In neurons the cadherins function as specifiers and as intercellular glue in the establishment of CNS synaptic connections, and in the mature brain, also appear to function in learning and memory events.

Ellen Barker, J. Henley, and G. Collingridge

Defining roles of PKMζ in AMPAR trafficking

MRC Centre for Synaptic Plasticity, Bristol University, Bristol, United Kingdom

Synaptic plasticity, the modulation of communication efficacy at synapses shapes the neural networks thought to encode memories. Long term potentiation (LTP), persistent enhancement of synaptic communication, is one such type of plasticity. LTP has two main mechanistically distinct phases, an induction (early) and a maintenance (late) phase (E-LTP, L-LTP) thought to be analogous to the processes of learning and long-term memory storage. AMPA receptors (AMPAR) mediate the majority of fast excitatory transmission in the brain, so changes in their synaptic expression underlie many forms of synaptic plasticity, with an increase in AMPAR number or conductivity leading to LTP. A brain-specific atypical Protein kinase C isoform PKMζ has been shown to be both necessary and sufficient for L-LTP, but not E-LTP. Perfusion of ZIP, a specific inhibitor of PKMζ into hippocampi of rats prevents memories of tasks persisting beyond about 10 minutes, and completely erases pre-established memories. As well as showing PKMζ is a key factor in memory formation, these studies provide evidence for links between the biphasic models of LTP and of memory formation. It was shown that blocking endocytosis of GluR2 in the amygdala of live rats prevents loss of memory associated with the application of ZIP, suggesting PKMζ maintains AMPAR at synapses by preventing GluR2-dependent endocytosis. I study the mechanisms of PKMζ-dependent AMPAR trafficking on a molecular level using cultured neurons. I show that ZIP decreases surface expression of GluR2 but not GluR1, although rates of endocytosis of both increase. GluR1 and GluR2 subunits have distinct roles and trafficking patterns in E-LTP and L-LTP, I hope to better define roles of PKMζ in the context of these phases by studying AMPAR behavior following endocytosis and identifying roles of other proteins involved.

Nora Mecklenburg, C. Sotelo,[2] and S. Martinez[1]

Cerebellar oligodendroglia have an extracerebellar origin

1 Instituto de Neurociencias (UMH-CSIC), Universidad Miguel Hernandez, Alicante, Spain; 2 Cátedra de Neurobiología del Desarollo Remedidos Caro Almela

While the origin of oligodendroglia in the prosencephalon and spinal cord has been extensively studied, the origin of cerebellar oligodendrocytes has been only partially analyzed. To investigate where cerebellar oligodendrocytes generate and which migratory pathways they follow to reach their adult ultimate locations, in-ovo transplants were performed using the quail/chick chimeric system. The chimeric embryos were developed up to HH45 (19 days) to map the localization of donor cells and analyze their phenotype by immunohistochemistry staining. We found that mesencephalic homotopic and homochronic transplants generated cellular migratory streams from the grafted epithelium into the host cerebellum, crossing the isthmic borders and entering to the cerebellum via the velum medullare into the ventral region of the central white matter. Mapping the final location of these mesencephalic cells showed that they are located in all layers of the cerebellar cortex except the external granular layer. From their entry into the cerebellum, they were mainly accumulated at the central and folial white matter, as well as in the superficial regions of the internal granular layer and around Purkinje cells. At this later location, the donor cells were positive for Vimentin and acquired Bergmann glial features. At the other locations, particularly in the white matter, they were positive for PLP and Olig2 with oligodendrocytic identity. The combinatory analysis of the different grafts allowed us to propose a fate map of chick cerebellar oligodendroglia at neural tube stage. Most oligodendrocytes originate from the central alar plate of the mesencephalic vesicle.

Anna Soriguera Farrés,[1] S. Bardehle,[1] S. A. Hoffmann,[1] J. M. Swiercz,[2, 3] S. Offermanns,[2, 3] J. Chun,[5] R. Nitsch,[1, 4] and A. U. Bräuer[1]

PRG-1 regulates N-Ras activity depending on extracellular LPA levels during axon growth

1 Institute of Cell Biology and Neurobiology, Center for Anatomy, Charité – Universitätsmedizin Berlin; 2 Institute of Pharmacology, University of Heidelberg; 3 Max Planck Institute for Heart and Lung Research, Bad Nauheim; 4 Institute for Microscopic Anatomy and Neurobiology, Universitätsmedizin der Johannes-Gutenberg-Universität; 5 The Scripps Institute, San Diego, USA

Plasticity-Related Gene-1 (PRG-1) has been shown to regulate LPA signaling and be involved in mechanisms of activity-dependent and structural plasticity in the brain. Furthermore, PRG-1 acts specifically at the excitatory synapse on neurons and has been recently proposed as an important player in the modulatory control of excitability via non-enzymatic control of extracellular LPA. PRG-1 contains nonconservative changes in the enzymatic-catalytical extracellular domains and has a unique hydrophilic C-terminus of around 400 amino acids. We found an interaction between PRG-1 and Ras GRF-2 through phospholipids during neuronal differentiation, which was disrupted by increased extracellular LPA. Intracellular signaling analysis on primary neurons showed phosphorylation of MAPK levels and enhanced MEK/ERK activation after LPA application. Furthermore, we identified a direct interplay between LPA levels, PRG-1 interaction and the activation of N-Ras protein, and specifically the application of LPA resulted in a significant increase in axon growth. Our experiments also show that PRG-1 is a Ras cascade controller during brain development.

SESSION 2

Tuesday, 2 November 2010

11.15 **Tor D. Wager**
The origins of pain in the central nervous system: Insights from manipulations of expectation and affective value

12.15 **Ryszard Auksztulewicz**
Thorsten Kahnt
Soyoung Q Park
› Ph. D. talks

Introduction **Hauke R. Heekeren**
Cluster of Excellence Languages of Emotion
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Chair **Christoph Korn**
Berlin School of Mind and Brain

Tor D. Wager

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present	Associate Professor of Psychology, The University of Colorado, Boulder
2004–2009	Assistant Professor of Psychology, Columbia University
2003	Visiting Research Fellow, The University of Michigan
1997–1998	Postgraduate Research Assistant, The University of Colorado, Boulder

Tor D. Wager

The origins of pain in the central nervous system: Insights from manipulations of expectation and affective value

Department of Psychology and Neuroscience, The University of Colorado, Boulder

Pain is a subjective experience created by a combination of noxious sensory input from the body and ongoing brain processes. Though a number of brain regions respond consistently to noxious input, it is still unclear how patterns of activity in different brain systems combine to generate pain. Likewise, though it is now widely recognized that pain is influenced by expectations, emotions, and other cognitive factors, it is still unclear how this information is represented in the brain, and where and how it is combined with signals from the body. We have approached these questions using a combination of fMRI, PET opioid binding, ERP, pharmacological MRI, and meta-analyses of neuroimaging studies of pain and emotion. In this talk, I will draw on this work to address two questions:

1) Does brain activity distinguish between physical and emotional "pain," and are there patterns that are specific to physical pain?
2) How do expectations about pain influence brain responses to painful events, and do they impact areas thought to be important for representing physical pain?

Ryszard Auksztulewicz,[1, 2] B. Spitzer,[3, 4] and F. Blankenburg[1, 3, 4]

Somatosensory working memory impairment by applying rTMS to the inferior frontal gyrus

1 Berlin School of Mind and Brain; 2 Institute of Psychology, Humboldt-Universität zu Berlin; 3 Bernstein Center for Computational Neuroscience Berlin; 4 Department of Neurology, Charité – Universitätsmedizin Berlin

Neural activity believed to subserve somatosensory working memory (SWM) has been found in several cortical regions in both humans and monkeys. One prominent area whose ongoing activity has been associated with SWM has been the inferior frontal gyrus (IFG). However, as previous studies have almost exclusively used correlational analyses, no clear evidence has so far been provided for the causal role of specific areas. Therefore, the question whether sustained neural activity in IFG is causally involved in a successful maintance of information in SWM remains unanswered.

Thorsten Kahnt,[1, 2] J. Heinzle,[1] S. Q Park,[2, 3] and J.-D. Haynes[1, 2]

Locally distributed coding of expected value and reward variability in multi-attribute decision making

1 Bernstein Center for Computational Neuroscience Berlin; 2 Berlin School of Mind and Brain; 3 Cluster of Excellence Languages of Emotion, Freie Universität Berlin

An optimal choice among alternative behavioral options requires precise anticipatory representations of their possible outcomes. A fundamental question is how such expected outcomes are represented in the brain. Using a combination of multivariate pattern classification and fMRI we have recently shown that the reward value of sensory cues can be decoded from distributed fMRI patterns in the medial OFC. This distributed representation is compatible with previous reports from animal electrophysiology which show that reward is encoded by different neural populations with opposing coding schemes. However, most behavioral options have more than one reward predictive attribute. Thus, the reward predictions of multiple attributes need to be integrated into a combined expected value. Here we address where the brain encodes the combined reward prediction and where it encodes the variability of the reward predictions of the individual attributes. We acquired fMRI data while subjects performed a task in which they had to integrate reward predictions from multiple attributes into a combined value. Using time-resolved support vector regression we find that (1) the combined value is encoded in distributed fMRI patterns in the medial OFC and that (2) the variability of value predictions of the individual attributes is encoded in the dorsolateral prefrontal cortex (dlPFC). These results demonstrate that the different features defining multi-attribute objects are encoded in non-overlapping brain regions and therefore suggest different roles for OFC and dlPFC in multi-attribute decision making.

Soyoung Q Park,[1, 2, 3] T. Kahnt,[3, 4] J. Rieskamp,[5] and H. R. Heekeren[1, 2, 3]

Neurobiology of value integration: When value impacts valuation

1 Department of Education and Psychology, Freie Universität Berlin; 2 Neurocognition of Decision Making Group, Max Planck Institute for Human Development, Berlin; 3 Berlin School of Mind and Brain; 4 Bernstein Center for Computational Neuroscience Berlin; 5 Department of Psychology, University of Basel

In everyday situations, we usually face multi-attribute decision options. Here the attributes are qualitatively different and can implicate either losses (e.g., costs to buy a bike) or gains (e.g., technical benefit of a bike). It has been suggested that these attributes values are integrated into a unified value currency to facilitate successful choice behavior (Montague and Berns, 2002; Heekeren et al., 2008). However, the exact neural mechanism of this value integration is still unknown. For decades, behavioral studies have assumed that the attributes' value contribute independently to the overall subjective value. However, human behavior violates this assumption, implicating interactions between values. We investigated 24 healthy male subjects using functional magnetic resonance imaging (fMRI) with a task involving choices with multi-attribute options that consist of visual cues indicating physical pain (electrical pulse) and monetary reward. Different subjective-value models made similar predictions of choice-behavior, suggesting that behavioral data alone is insufficient to uncover the underlying integration mechanism. In contrast a direct model comparison on brain data decisively demonstrated that interactive value integration predicts neural activity significantly better than the independent mechanism. These results provide novel insights into the neurobiological underpinnings of human decision making involving the integration of different values.

SESSION 3

Tuesday, 2 November 2010

15.00 **Eero P. Simoncelli**
Bayesian modeling of visual motion perception

16.00 **Jan Clemens, Hannah Dold, Evelin Wacker**
› Ph. D. talks

Introduction **Felix Wichmann**
Bernstein Center for Computational Neuroscience Berlin

Chair **Kai Görgen**
International Doctoral Program Computational Neuroscience

Eero P. Simoncelli

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2006–present	Professor, Departments of Neural Science, Mathematics, and Psychology, New York University (Associate Professor, 1999–2007; Assistant Professor, 1996–1999)
2000–present	Investigator, Howard Hughes Medical Institute
1993–2000	Assistant Professor, Computer and Information Science, University of Pennsylvania (Adjunct Professor, 1996–2000)
1987–1993	Research Assistant, Vision Science Group (now called the Vision and Modeling Group), MIT Media Laboratory
1990 and 1991	Research Contractor, NASA-Ames Research Center, Human Factors Division, Vision Group

Eero P. Simoncelli

Bayesian modeling of visual motion perception

Departments of Neural Science, Mathematics, and Psychology, New York University, New York, USA

I will describe our recent efforts to explain the perception of local retinal image motion as resulting from a process of optical statistical inference. Specifically, I will show that a Bayesian model can provide a quantitative explanation of human subject behavior in tasks involving the estimation of speed, direction, or coherence of a moving pattern. I will also discuss our current hypotheses regarding the physiological underpinnings of these results.

Jan Clemens,[1, 2] S. Schreiber,[2, 3], O. Kutzki,[1, 2] B. Ronacher,[1, 2] and S. Wohlgemuth[1]

Transformation of the population code in the auditory pathway of grasshoppers

1 Department of Biology, Behavioral Physiology Group, Humboldt-Universität zu Berlin; 2 Bernstein Center for Computational Neuroscience Berlin; 3 Institute for Theoretical Biology, Humboldt-Universität zu Berlin

How does the neural representation of the sensory environment change at successive steps in a sensory pathway? What is the function of each processing step?

We tackled these questions within the auditory system of grasshoppers. These small insects rely on acoustic cues to recognize, evaluate and localize mates. Although the grasshopper's auditory system is simple, it performs tasks comparable to some of those fulfilled by the much more complicated auditory system of vertebrates. The first steps of auditory processing in grasshoppers are organized in a simple three-layer network: The input layer of receptors transforms the acoustic stimulus into neural spike trains. The two subsequent layers perform important pre-processing steps before perceptual decisions are made in the brain.

In order to learn about the function of these last two steps, we tracked the neural representation of the natural song of grasshoppers in terms of the precision and the information content of neuronal responses. In addition, we compared the diversity of the feature selectivity of neurons within each layer.

Our results show that the intermediate layer in the network acts as a hub that enhances the fidelity of the neural representation by pooling responses from many auditory receptors. Cells in the output layer exploit this highly informative input to extract specific, possibly behaviorally relevant features of the song. This in turn enables the grasshopper's brain to perform those pattern recognitions tasks that are necessary to successfully find an appropriate mate.

Hannah M. H. Dold, I. Fründ, and F. A. Wichmann

Bayesian estimation of shared parameters

Modelling of Cognitive Processes, Bernstein Center for Computational Neuroscience Berlin and Technische Universität Berlin

Experimental data are typically noisy, and one aspect of fitting a model to one's data is to parametrically describe the data and to see how different experimental conditions affect the model parameters. When comparing results from different experimental conditions we expect some model parameters to vary, but others to remain more or less constant. Sometimes we would even like to enforce that some parameters stay constant; in the following we term parameters that stay constant across experimental conditions "shared parameters."

In Bayesian estimation, each parameter is associated with a prior distribution and a posterior distribution, which describe the probability of a given parameter value before and after observing the data, respectively.

For shared parameters it is required that their posterior distributions under the different experimental conditions are highly overlapping. One solution to achieve the posterior distribution overlap is to choose suitable prior distributions. The key challenge is to find such priors without impairing the model fit significantly.

Here we present a two-step technique to estimate suitable prior distributions under a concurrency constraint and illustrate our technique using psychometric functions.

The posterior distributions obtained through the estimation procedure are highly overlapping and follow an analytically derived distribution. The goodness-of-fit remains comparable to goodness-of-fit obtained from estimation without the concurrency assumption, if the shared parameters actually originate from the same distribution. The proposed prior distributions are thus superior to so-called uninformative priors, but are chosen in a well defined way and do not reflect the scientist's prejudices or assumptions.

Evelin Wacker, R. Lützkendorf, B. Spitzer, J. Bernarding, and F. Blankenburg

Tactile motion and pattern processing assessed with high-field fMRI

Department of Neurology, Charité – Universitätsmedizin Berlin; Bernstein Center for Computational Neuroscience Berlin; Institute for Biometry and Medical Informatics, Otto-von-Guericke-Universität Magdeburg

Contrary to the extensive research on processing of motion and form in the visual domain, the specific neuronal pathways underlying perception of tactile presented stimulus properties remain poorly understood. Here, we used ultra-high-field functional magnetic resonance imaging (fMRI) to investigate the neuronal correlates of tactile motion and pattern processing in humans. Different types of dynamic Braille stimuli were delivered to participants' index finger, creating the sensation of moving or stationary bar patterns during passive touch. In line with previous work, activity in early somatosensory cortex was increased both during motion and pattern processing, respectively, compared to physically matched control conditions. Moreover, we found evidence for motion directionality encoding in primary and secondary somatosensory cortices (SI and SII), as well as for pattern orientation encoding in the intraparietal sulcus (IPS). Beyond, in higher cortical areas, tactile motion induced activity in the middle temporal cortex (hMT+/V_5), whereas tactile pattern processing engaged the supramarginal gyrus (SMG). The specific responses in these areas covaried with subjects' ability to identify moving and patterned stimuli, respectively, suggesting that hMT+/V_5 and SMG may in particular contribute to conscious perception of complex tactile stimulus features. Interestingly, an analysis of effective connectivity further revealed increased functional coupling between SI and hMT+/V_5 during motion processing, as well as between SI and SMG during pattern processing. This provides evidence for a direct integration of specialized higher-level cortical areas into tactile processing circuits during somesthesis.

SESSION 4

Wednesday, 3 November 2010

09.00 **Richard Miles**
Hippocampal synchrony in disinhibited guinea-pig slices and human epileptic tissue

10.00 **Anna Maslarova**
Etienne Ndzié Atangana
Ranjeet Verma
› Ph. D. talks

Introduction **Uwe Heinemann**
Charité – Universitätsmedizin Berlin

Chair **Seda Selar**
International Graduate Program Medical Neurosciences

Richard Miles

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Richard Miles began his postdoctoral work with RKS Wong in Galveston, TX trying to understand how recurrent excitatory connections between hippocampal pyramidal cells produce epileptiform synchrony. Collaboration on simulations of population activities with RD Traub (then at IBM) convinced him that data was needed on the properties of hippocampal synapses. In records from pairs of cells, Dr Miles studied the synaptic excitation of pyramidal and inhibitory cells and the inhibition of pyramidal cells as well as poly-synaptic inhibitory and excitatory circuits. This work suggested that di-synaptic inhibition normally controls the spread of activity via poly-synaptic excitatory circuits and that removing this control leads to synchrony.

After moving to Paris, Dr Miles examined the morphological substrate of synaptic interactions between pairs of CA3 neurones in collaboration with the group of TF Freund (Budapest). This work showed that some excitatory synapses possess a single release site, and revealed a diversity of hippocampal inhibitory cells with distinct functions. Moving back to population activities, Richard Miles examined differences between EPSP – spike coupling in pyramidal cells and interneurons with D Fricker and explored extracellular approaches to ensemble discharges with I Cohen. Collaboration with clinicians at the Pitié-Salpêtrière hospital in Paris offered an opportunity to examine the generation of synchrony in human epileptic tissue. Recent data suggests that an unexpected region – the subiculum – and an unexpected mechanism – depolarising GABAergic signalling – are involved in the generation of human interictal activities.

Richard Miles

Hippocampal synchrony in disinhibited guinea-pig slices and human epileptic tissue

Institut National de la Santé et de la Recherche Médicale (INSERM), U975, Cortex & Epilepsy Group, Paris, France

I will compare the generation of synchronous population burst firing in a slice model – the CA3 region of the hippocampus when GABAA receptor mediated inhibition is suppressed – and in slices prepared after operations to remove focal tissue from patients suffering from temporal lobe epilepsies.

Disinhibition induced synchrony depends on the recurrent excitatory synaptic network that connects intrinsically burst firing CA3 pyramidal cells. It occurs in small tissue pieces containing 2–4000 pyramidal cells. We have shown that a population burst is initiated when summed neuronal activity exceeds a threshold. This threshold behavior depends on a balance between glutamatergic signalling and slower inhibitory signals mediated by GABAB receptors. Population bursts are initiated at a specific pacemaker site in the CA3 region, where cells are somewhat more excitable and recurrent excitatory connectivity is higher.

Interictal-like epileptiform activity in human tissue depends not only on recurrent excitation, but also on depolarising signalling mediated by GABAA receptors. In human tissue the CA3 and CA1 regions of the hippocampus are sclerotic but the subiculum generates spontaneous population discharges that are similar to EEG records from the same patients. About 20% of subicular cells participate in these discharges and in these cells GABAergic signals are depolarizing due in part to a loss of the K-Cl cotransporter KCC2.

Seizure-like activities lasting for several 10s of sec can be initiated in human epileptic tissue by multiple convulsants. While interictal-like activity probably depend on a defect in basal Cl-homeostasis, ictal-like events may result from a loss of Cl-homeostasis during high-frequency activation of inhibitory synapses. An activity dependant switch in GABAergic signalling, coupled with excitatory synaptic actions and extracellular K accumulation may generate the prolonged depolarization that underlies a seizure.

Anna Maslarova, A. Wahab, and U. Heinemann

How does the M-type potassium channel affect excitability in the epileptic entorhinal cortex?

Institute of Neurophysiology, Charité – Universitätsmedizin Berlin

The cholinergic hypothesis of epilepsy assumes a key role of acetylcholine-related genes and proteins in the mechanisms underlying chronic temporal lobe epilepsy. Some candidates are the acetylcholine esterase, muscarinic receptors and reduced acetylcholine levels. Less studied in this context are voltage-gated potassium channels of the Kv7 family, also known as M-type channels, because they can be indirectly blocked by muscarine-receptor agonists.

We performed extracellular field recordings from acute temporo-hippocampal slices to investigate the effect of acetylcholine and of a specific Kv7 channel blocker on spontaneous firing in the entorhinal cortex. We compared the effects in two animal models of chronic temporal lobe epilepsy: intrahippocampal kainate application in mice and intraperitoneal pilocarpine injection in rats. In both models an acute status epilepticus is followed by the development of chronic epilepsy.

In the entorhinal cortex of non-epileptic control animals, neither acetylcholine 20μM nor the specific Kv7 blocker linopirdine 20μM induced any epileptiform activity. In the kainate-treated mice application of acetylcholine or linopirdine was followed by interictal spikes in the entorhinal cortex. In the pilocarpine treated rats, acetylcholine and linopirdine induced ictal spiking and seizure-like events in the entorhinal cortex with propagation to the subiculum.

Our results demonstrate that acetylcholine and the specific Kv7 blocker linopiridne affect the activity in chronic epileptic entorhinal cortex in a similar fashion, which implies a change in function of the M-type current. Because the effect is absent in the normal brain, it is possible that the change is part of a compensatory mechanism against overexcitability in the epileptic brain.

Etienne Ndzié Atangana, U. C. Schneider, and P. Vajkoczy

Inflammation in the brain after subarachnoid hemorrhage (SAH): role and possible intervention

Experimental Neurosurgery, Charité – Universitätsmedizin Berlin

Hemorrhage into the subarachnoid space, elicits an as yet poorly understood cascade of events leading to brain injury and poor outcome in patients. The mechanisms of this brain injury clearly differ from those underlying brain injury after ischemia or trauma in that they are more complex, and less well understood. Recent clinical, biological and experimental findings have brought more and more evidences suggesting that an inflammatory response within the CNS after the onset of the subarachnoid hemorrhage should be the starting point to explain numerous complications related to the SAH, such as vasospasm for example. This inflammation could also contribute directly to the brain injury.

Critical steps in the pathological cascade of an inflammatory response within the CNS are the recruitment of circulating immune cells to the brain and the activation of resident CNS immune cells. Homing of immune cells to sites of injury or inflammation represents a multistep process which comprises the tethering of circulating leukocytes to the vessel wall, their subsequent transendothelial and interstitial migration, mediated by cell adhesion molecules, such as selectins and integrins.

Our research is focused on this multistep process of recruitment and activation of circulating and resident immune cells to and within the CNS, following a surgically induced subarachnoid hemorrhage on Wild-type mice and knockout models such as Del-1 -/- and Ang-2-/- Mice. Our first immunhistochemistry (IHC) and in-vivo microscopy (IVM) results could support the important role of leucocytes-induced inflammation in the brain after SAH.

Ranjeet Verma,[1, 2] F. Ebstein,[1] S. Prokop,[2] A. Halle,[2] A. Lehmann,[1] F. Heppner,[2] and P. M. Kloetzel[1]

The impact of immunoproteasome in neurodegenerative disease

1 Institute of Biochemistry, Charité – Universitätsmedizin Berlin; 2 Institute of Neuropathology, Charité – Universitätsmedizin Berlin

The close relationship between neurodegeneration and the ubiquitin proteasome system (UPS) has long been implicated through the consistent findings of ubiquitin-positive protein aggregates in various neuropathological studies. In fact, the observation of ubiquitinated-protein inclusion bodies is one of the hallmarks of neurodegeneration. Damaged proteins can accumulate under certain adverse conditions like oxidative stress, protein misfolding, mutations, aging and so on. The UPS represents the major ATP dependent protein degradation system in eukaryotes that is involved in the maintenance of cellular protein homeostasis. Under the influence of immune response certain β subunits namely LMP2 (β1i), MECL-1 (β2i) and LMP7 (β5i) can replace constitutive β1, β2, and β5 subunits of catalytic 20S core of UPS, resulting in a new complex referred to as immunoproteasomes (IPs) (1). IPs exhibit altered, elevated peptidase activity and cleavage site preferences resulting in more efficient liberation of many MHC class 1 epitopes (2). IPs has potential to clear oxidant damaged proteins in IFN induced oxidative stress (3). However nothing much is known about them in neurodegenerative disease. It is important to investigate the role of IPs in Neurodegenerative diseases.

SESSION 5

Wednesday, 3 November 2010

13.30 **Lutz Birnbaumer**
Signal Transduction by G Proteins: Focus on molecular aspects of activation and deactivation of a regulatory GTPase and the role of Mg ion

14.30 **Jens Baron**
Chia-Ling Chang
Agustin Liotta
› Ph. D. talks

Introduction **Gudrun Ahnert-Hilger**
Charité – Universitätsmedizin Berlin

Chair **Gürsel Çalışkan**
International Graduate Program Medical Neurosciences

Lutz Birnbaumer

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At NIEHS (NIH, DHHS), Research Triangle Park, North Carolina

2001–2007	Senior Investigator (Full Professor equivalent)
2001–2006	Scientific Director, Division of Intramural Research, NIEHS, NIH and DHHS
2001–2007	Head, Transmembrane Signalling Group, Laboratory of Signal Transduction, DIR, NIEHS
present	Head, Transmembrane Signalling Group, Laboratory of Neurobiology, NIEHS

At UCLA, Los Angeles, California

1994–2001	Professor, Department of Anesthesiology, School of Medicine
1994–2001	Professor, Department of Biological Chemistry, School of Medicine
1996–2000	Director, Embryonic Stem Cell and Transgenic Mouse Facility, UCLA Jonsson Comprehensive Cancer Center
1997–2001	Professor and Chair, Department of Molecular, Cell and Developmental Biology, College of Letters and Science

At Baylor College of Medicine, Houston, Texas

1975–1994	Professor, Department of Cell Biology,
1986–1994	Professor, Department of Physiology and Molecular Biophysics,
1990–1994	Professor, Division of Neurosciences
1992–1994	Director, Diabetes Research Center, Department of Medicine
1993–1994	Professor, Department of Medicine (Endocrinology)

Lutz Birnbaumer

Signal Transduction by G Proteins: Focus on molecular aspects of activation and deactivation of a regulatory GTPase and the role of Mg ion

Laboratory of Neurobiology, National Institute of Environmental Health Sciences, NIH, DHHS, North Carolina, USA

The evolution of our knowledge about the way Mg^{2+} participates in the activation of heterotrimeric G proteins will be reviewed, beginning with its requirement in hormonal stimulation of fat cell adenylyl cyclase (1969), the development of the "signal transduction by G proteins" concept and ending with knowledge that incorporates information obtained from site directed mutagenesis and examination of the crystal structures of G proteins (2010). Our current view is that G protein coupled receptors act as exchange factors that allow free exchange of GTP for GDP, and that, as it seeks to fill its octahedral coordination shell, Mg acts as a keystone locking the GTP into its binding pocket and the G protein's alpha subunit into a conformation in which Gα dissociates from the Gβγ dimer and becomes competent in regulating effectors. The Gα also acquires the GTPase activity without which it would not deactivate. GTPase activation is the result of moving the backbone carbonyl group of the Mg-coordinating threonine into a location in space that positions the hydrolytic water so as to facilitate the water's nucleophilic attack that leads to hydrolysis of the link between the β and γ phosphates of GTP. The role of the backbone carbonyl group of the Mg-coordinating threonine is equihierarchical with a similar and long recognized role of the Switch II glutamine γ amide carbonyl group, whose disruption leads to loss of GTPase activity.

Jens Baron, H. Hörtnagl, L. Birnbaumer, G. Ahnert-Hilger, and I. Brunk

Go1 protein subunit alpha as an important regulator of the dopaminergic system crucial for survival

Center for Anatomy, Integrative Neuroanatomy, Charité – Universitätsmedizin Berlin

The dopaminergic system is known to be linked to diseases like depression and Parkinson's disease. To better understand how underlying cellular pathways lead to these missregulations of brain function, it is of great importance to find new players that are involved in regulating the dopaminergic system. Previous data proposed the alpha subunit of Go protein as one of these regulators, as Go alpha is the major G protein coupled to D2 dopamine receptors. The Go alpha subunit is encoded by a single transcript, that is alternatively spliced into two isoforms, entitled Go1 alpha and Go2 alpha, respectively. Our work established Go2 alpha as a key regulator in vesicular uptake of monoamines, like serotonin and dopamine, by regulating vesicular monoamine transporter (VMAT) activity in brain. While Go2 alpha -/- mice appear to be phenotypically normal, Go1 alpha -/- and Go alpha double knock out (Go1/2 alpha -/-) mice are growth retarded and display a reduced lifespan. Furthermore, these animals reveal reduced motor activity on a rotating rod compared to wild type and Go2 alpha -/- mice. On a molecular level Go1 alpha -/- mice show increased dopamine levels in striatum and Go2 alpha expression is significantly augmented. Here we demonstrate, that Go1 alpha is not only the more abundant form in mouse brain compared to Go2 alpha, but also an important regulator of the dopaminergic system. Under influence of Go1 alpha a disturbed balance in favour of Go2 alpha appears to decrease motor activity, growth and lifespan, although the striatal dopamine level is raised.

Chia-Ling Chang and C. Rosenmund

General rules for autapse and heterosynapse formation and function in mini neuronal circuits

International Graduate Program Medical Neurosciences; Cluster of Excellence NeuroCure, Charité – Universitätsmedizin Berlin

The interplay between glutamatergic (glu) and GABAergic (GABA) neurons via synaptic connections is critical for virtually all synaptic circuitries in the central nervous system. The diversity of cell types and synaptic properties in different brain regions results in a wide variety of synaptic plasticity characteristics and functions. To study the underlying basic principles and putative cell-autonomous mechanisms determining presynapse release, we employed a reduced cell-culture system using hippocampal and striatal neurons from newborn mice, in which either one or two neurons from each region were grown on microglial islands. We first tested whether the neurons preferentially formed autapses or heterosynapses by measuring the response of the postsynaptic currents (PSCs). The PSCs of the autapses was significantly larger than those of heterosynapses in three kinds of pairs (hippocampal glu-glu, GABA-GABA and striatal GABA-GABA). Additionally, the vesicle release probabilities (Pvrs) and paired-pulse facilitation were similar for autaptic and synaptic connections in both hippocampal glu-glu and striatal GABA-GABA pairs. However, in hippocampal Glu-GABAergic pairs, the Pvrs of GABAergic autapses and heterosynapses were significantly lower than those of single GABAergic neurons and GABA-GABA synapses, indicating that the presence of glutamatergic neurons modulated release probability in GABAergic nerve terminals. We also determined whether the pre- or postsynaptic neuron is instructive by correlating their individual behaviors in Pvr and, using paired-pulse ratios (PPRs), short-term plasticity. These results indicate that neurons don't show resistant to form autapse and neurons have the capacitance to form a certain number of synapses in this culture system and that the presynaptic neuron is predominantly instructive for short-term plasticity characteristics.

Agustin Liotta,[1] G. Çalışkan,[1] R. ul Haq,[1] J. O. Hollnagel,[1] A. Rösler,[1] U. Heinemann,[1, 2] and C. J. Behrens[1]

Partial disinhibition is required for transition of stimulus-induced sharp wave-ripple complexes into recurrent epileptiform discharges in rat hippocampal slices

1 Institute of Neurophysiology, Charité – Universitätsmedizin Berlin; 2 Cluster of Excellence NeuroCure, Charité – Universitätsmedizin Berlin

Hippocampal sharp wave-ripple-complexes (SPW-Rs) are characterized by slow field potential transients superimposed by ~200 Hz ripple oscillations. Similar events have been recorded in hippocampal slices where SPW-Rs occur spontaneously or can be induced by repeated application of high frequency stimulation (HFS). Such stimulation is reminiscent of protocols used to induce kindling epilepsy, and ripple oscillations may be predictive of the epileptogenic zone in temporal lobe epilepsy. In the present study, we investigated the relation between recurrent epileptiform discharges (REDs) and SPW-Rs by studying effects of partial removal of inhibition. In particular, we compared the effects of nicotine, low-dose bicuculline (BMI) and elevated extracellular potassium concentration ($[K^+]o$) on induced SPW-Rs. We show that nicotine dose-dependently transformed SPW-Rs into REDs. This transition was associated with reduced inhibitory conductance in CA3 pyramidal cells. Similar results were obtained from slices where the GABAergic conductance was reduced by application of low concentrations of BMI (1–2 µM). Elevating [K+]o from 3 to 8.5 mM did not transform SPW-Rs into REDs but significantly increased their incidence and amplitude. Under these conditions, the equilibrium potential for inhibition was shifted in depolarizing direction, while inhibitory conductance was significantly increased. In conclusion, recruitment of inhibitory cells during SPW-Rs may serve as a mechanism by which hyperexcitation and eventually seizure generation might be prevented.

POSTERS

Tuesday, 2 November 2010

13.45–15.00 **odd numbers**

Wednesday, 3 November 2010

10.45–12.00 **even numbers**

Foyer of the Conference Center MDC.C

Katja Blazej, J. Ladhoff, H. Radbruch, N. Gladow, F. Fernandez-Klett, J.-U. Peter, and J. Priller

Characterization of the LysM-Cre×IKK2fl/fl mouse

P1

Molecular Psychiatry, Department of Experimental Neurology, Charité – Universitätsmedizin Berlin

In the CNS, microglia and perivascular macrophages are the main players in innate immunity and their role in inflammatory and degenerative disorders of the brain is still poorly understood. A key regulator of inflammation and activation of microglia is nuclear factor (NF)-κB. It controls proinflammatory gene expression and is activated by a protein complex including IκB kinase (IKK) 2. To aim inhibition of microglia and macrophage activation by blockade of the NF-κB signalling pathway, we created mice, in which the IKK2 gene is deleted in the myeloid cell lineage. Using the Cre-loxP technology, we crossed mice expressing Cre recombinase under the control of the Lysozyme M promoter (LysM) with mice carrying two loxP-flanked (floxed) IKK2 alleles. In this conditional LysM-Cre×IKK2fl/fl knock-out mouse, we observed a 90% decrease of IKK2 mRNA expression in macrophages, whereas 40 to 80% reduction was quantified in the IKK2 protein expression in microglia and macrophages. LPS-induced nuclear translocation of the NF-κB subunit p65 was reduced in microglia isolated from this mouse. Furthermore, secretion of cytokine TNF-α after LPS-stimulation was found to be attenuated to one third in primary microglia and to 62% in peritoneal macrophages isolated from the LysM-Cre×IKK2fl/fl mouse, as well as microglial production of nitric oxide was downregulated to 50% in vitro. Under normal conditions no difference of immune state and phagocytotic ability of microglia was found compared to wild type littermates. Taken together, our results show that LysM-Cre×IKK2fl/fl knock-out mice may be a useful tool to study the role of microglia and macrophages in CNS inflammation and degeneration.

Larisa Bulavina, K. Färber, V. Matyash, and H. Kettenmann

P2 Modulation of microglia immune functions by purines

Department of Cellular Neurosciences, Max Delbrück Center for Molecular Medicine Berlin-Buch

In our study we analyzed the functional role of CD39 activity for microglial phagocytosis. CD39 is a microglia-specific ectoenzyme, which hydrolyzes ATP, released from damaged tissue, to ADP and AMP (Zimmermann, 2006). To monitor the phagocytic activity of ramified microglia from adult mice and ameboid microglia from postnatal day 6 to 9, we applied opsonized fluorescent latex beads to acute brain slices from CD39WT and KO mice. We found that basal phagocytic activity of adult microglia from CD39KO mice is higher as compared to the WT. There was no difference between P6-P9 phagocytosis in CD39 WT versus KO microglia. However, basal phagocytosis in P6-P9 ameboid microglia was significantly higher then those of adult CD39WT, emphasizing the developmental differences in microglia physiological activity.

Additionally, we compared the responses of microglia to laser lesion in acute slices from adult CD39KO mice to the WT animals. To visualize microglial motility in brain slices, CD39KO animals were crossed with mice expressing EGFP under microglia-specific CX3CR promoter. Laser lesion causes the quick movement of microglia processes towards the lesion, which has been described to be mediated by ATP released from damaged cells (Davalos et al., 2005). In the brain slices from CD39KO animals, the microglial response to the injury was either very slow or completely abrogated. We also observed that microglial cells had a different morphology in acute slices of animals resembling more an activated state. This could be quantified by a larger soma area of CD39KO microglial cells as compared to wild type.

Anne L. Dätwyler,[1] G. Lättig,[1] A. Kunz,[1] W.Yang,[2] W. Paschen,[2] U. Dirnagl,[1] M. Endres,[1] and C. Harms[1]

Elucidating the function of SUMO2/3 in neurons after ischemic stress

P3

1 Center for Stroke Research Berlin; 2 Department of Anesthesiology, Duke University Medical Center, Durham, United Kingdom

The posttranslational protein modification through members of the SUMO (small ubiquitin like modifier) family impacts on localization, binding affinity and stability of their targets. SUMO conjugation is activated in cultured cells by various stress conditions, including hypo- and hyperthermia and oxidative stress. Thus, sumoylation may be a conserved endogenous protective cell response induced under stress conditions. In this work we aimed to elucidate the function of SUMO2/3 on neuronal cell fate after hypoxic stress by using an in vitro model of ischemic stress, the oxygen-glucose deprivation (OGD). We analyzed the kinetics of SUMO induction and found a peak of sumoylated target proteins three hours after OGD.To investigate whether sumoylation is essential for the survival of cells after ischemic stress, we performed a neuronal specific loss-of function approach using microRNA against SUMO2/3 driven by a neuronal specific promoter. In a damage titration assay using different OGD lengths, we could show that lentivirally mediated knockdown of SUMO2/3 leads to dramatically increased vulnerability of neurons. In a gain-of function approach we show that neurons exposed to OGD can be protected by reintroducing a silent mutated form of SUMO2/3. This myc-tagged overexpression construct also enables us to screen for sumoylation targets after ischemic stress through tandem affinity purification (TAP) and a proteomics approach.

Odilo Engel,[1] C. Meisel,[1] S. Shenhar-Tsarfaty,[2] A. Goncalves,[4] M. Thielke,[1] M. Soreq,[3] and A. Meisel[1]

P4 Vagal activation is a key player in immunodepression after stroke

1 Department for Experimental Neurology, Charité – Universitätsmedizin Berlin; 2 Departments of Neurology and Internal Medicine D, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel; 3 The Institute of Life Sciences and the Interdisciplinary Center of Neuronal Computation, The Hebrew University of Jerusalem, Jerusalem, Israel; 4 Max Delbrück Center for Molecular Medicine Berlin-Buch

Despite improved stroke care on specialized stroke units, stroke-associated infections, e.g. pneumonia, remain frequent and prognostic relevant clinical complications. Previously, we have identified a CNS-injury-induced immunodepression syndrome (CIDS) in an experimental model of focal cerebral ischemia (MCAO) leading to spontaneous systemic bacterial infections within 3 days after stroke. (Meisel et al. 2005; Dirnagl et al. 2007)

A growing body of evidence suggests that acute CNS injury destabilizes the well-balanced interplay between the nervous and immune systems leading to the descibed immunodepression. Previously we could show that the sympathetic nervous system and the hypothalamo-pituitary-adrenal-axis are involved in the events after CNS-injury. (Prass et al. 2003, Meisel et al. 2005)

Here we show first evidence for the involvement of the parasympathetic nervous system in immunodepression after stroke, suggesting an overactivation of this pathway. Vagotomised animals showed significantly less bacterial growth in the lung after experimental stroke compared to sham-vagotomised, and showed a better functionality with respect to the immune cells. We observed similar results in alpha7-knockout-mice, indicating that this receptor is mainly involved in these events. Furthermore not only the secretion of the transmitter acetylcholine changes after stroke, but also the expression of its cleaving enzyme acetylcholinesterase.

Uldus Khojasteh, M. Foddis, D. Harhausen, J. König, U. Dirnagl, and C. Trendelenburg

Analysis of the functional relevance of the inflammasome component ASC in experimentally induced focal cerebral ischemia in mice

P5

Experimentelle Neurologie, Charité – Universitätsmedizin Berlin

Cerebral ischemia elicits acute inflammation which exacerbates tissue damage and is involved in secondary brain damage. In stroke, proinflammatory cytokines, especially interleukin (IL)-1beta, are activated by caspase-1. It is itself activated by the inflammasome which assembles dynamically in response to upstream intracellular components and cell injury. The soluble cytosolic adaptor protein ASC (apoptosis-associated speck-like protein containing a caspase recruitment domain) is a central binding partner for the other inflammasome components. However, an ASC-independent inflammasome has been described. In a previous study we have shown that ASC is expressed in the normal and postischemic brain. Mice were subjected to transient middle cerebral artery occlusion (MCAO). The results showed that ASC mRNA is up-regulated in the affected tissue after focal cerebral ischemia. In this study we used immunohistochemical analysis and showed ASC protein expression in microglia/macrophages, and increased staining of ASC in the ischemic tissue compared to the unaffected tissue. Surprisingly, we could not assess any significant difference of infarct volume or neurological score between groups of wildtype (WT) and ASC-deficient (ASC-/-) mice which underwent different MCAO models. In vitro experiments with peritoneal macrophages from WT and ASC -/- mice, however, revealed decreased levels of Il-1beta secretion in ASC-/- mice. These findings show that in the postischemic mouse brain ASC is up-regulated both on the mRNA and on the protein level but ASC-deficiency solely has no effect on infarct outcome parameters. One might conclude that in the stroke models used ASC is less important or caspase-1 and IL-1 beta are of minor significance.

Michael Kintscher, D. Schmitz, and J. Breustedt

P6 RIM1α controls short-term plasticity by setting release probability

Neuroscience Research Center, Charité – Universitätsmedizin Berlin

Changes in the strength of synaptic transmission are activity dependent and can be short- or long-term. Whereas long-term changes are due to a persistent alteration of presynaptic proteins and/or insertion of postsynaptic receptors, short-term plasticity (STP) is mostly determined by the composition and organisation of the presynaptic release machinery at the active zone.

Here we examine the role of RIM1α, a presynaptic protein of the active zone, in STP. The loss of this protein in RIM1α KO mice leads to an increased short-term plasticity at hippocampal Schaffer collateral – CA1 (SC-CA1) synapse and cerebellar parallel fiber – Purkinje cell (PF-PC) synapse.

By using electrophysiological means and pharmacology we show that the basic synaptic transmission is deceased at both synapses. This is accompanied by a reduction of the glutamat transient in the synaptic cleft. Performance of mean-variance analysis (MVA) revealed that this reduction can be explained by a lower release probability (Pr), whereas the quantal content (Q) is unchanged.

Min-Chi Ku, R. Glass, and H. Kettenmann

Interaction of glioma cells with intrinsic brain cells

P7

Max Delbrück Center for Molecular Medicine Berlin-Buch

Gliomas are the most common primary tumors of the central nervous system. Gliomas, like other solid tumors, are not a homogenous cellular mass, but contain many parenchymal cells, which have substantial impact on tumor progression. In the present study, we investigated soluble factors and related receptors by which glioma cells communicate with brain cells. We have demonstrated previously that glioma cells attracted neural stem cells and microglial cells into the tumor region. We now established a protocol to encapsulate glioma cells into a hollow fiber (HF) which allows the passage of diffusible molecules, but not cells.

With this model we can study the impact of released factors and exclude effects mediated by cell-cell contacts. The cells within these HF survived and expanded for at least 20 days after cell encapsulation as studied with morphological and histological assays. In vivo, preliminary experiments have shown that fibers with glioma cells attract massive amount of neural stem cells, microglial cells and GFAP positive astrocytes but not NG2 cells in the mouse brain as compared with controls (HF loaded with fibroblasts in contra lateral hemisphere). Small numbers of T cells were also found surround the glioma fiber. Furthermore, human glioma cells can also be entrapped in HF and implanted into mouse brain. Taken together, this approach may help us to identify factors by which these cell types communicate via soluble factors in a complex environment like gliomas.

Anna E. Kufner,*,[2], B. Hotter,*,[1] U. Malzahn,[1] G. J. Jungehulsing, and J. D. Fiebach[1]

P8 Can we trust negative diffusion-weighted imaging?

1 Center for Stroke Research, Charité – Universitätsmedizin Berlin; 2 International Graduate Program Medical Neurosciences; * Contributed equally

Patients with a negative acute DWI often remain a source of diagnostic uncertainty and can lead to doubt of the finding's reliability. A screening tool would be valuable to guide scarce resources towards patients who should receive a second scan to detect initially invisible infarction. We hypothesized that the NIHSS would be a good screening tool to determine whether a second MRI is necessary to determine infarction via DWI. Regardless of the final diagnosis, adult patients with suspected cerebral ischemia underwent acute and follow-up stroke MRI. All patients that had negative acute DWI were included in the analysis. We calculated odds ratios in order to determine the strength of association between a dichotomized NIHSS (0 vs. ≥1) and DWI restriction, and to determine possible confounders. We calculated the negative predictive value (NPV) to determine the NIHSS as a valid screening tool. 151 patients had negative acute DWI and were included in the analysis. 63 subjects received follow-up MRI scans, 7 had a positive DWI on the second day (11.1%). Median NIHSS on the following day after symptom onset for DWI positive and negative patients was 3.5 and 0, respectively. We found a strong association between the dichotomized NIHSS on the second day and DWI restriction (OR 17.50 95% CI 2.83-108.12). The NPV for the dichotomized NIHSS on the following day for infarction observed by DWI was 0.96. We found a borderline association for atrial fibrillation (OR 5.15 95% CI .95-27.98). The time to imaging showed a significance of $p = 0.1$ (Mann-Whitney-U-test). NIHSS on the following day remained significant even after Bonferroni adjustment for multiple testing. Conclusion: Based on our analysis, the NIHSS on the second day is a reliable screening tool to determine whether a second MRI is necessary to determine infarction via DWI.

Sabrina L. L. Lee,[1] G. Lättig,[1] K. Gertz,[2] G. Kronenberg,[2] U. Harms,[2] M. Balkaya,[2] A.-L. Dätwyler,[1] J. An,[3] S. Donath,[3] M. Endres,[1] and C. Harms[1]

Impact of apoptosis repressor with caspase recruitment domain (ARC) protein delivery on stroke outcome

P9

1 Center for Stroke Research, Charité – Universitätsmedizin, Berlin; 2 Department of Neurology, Charité – Universitätsmedizin Berlin; 3 Max Delbrück Center for Molecular Medicine Berlin-Buch

The ARC protein has been shown to protect against oxidative stress-induced apoptosis by interfering with the death receptor dependent and the mitotic signaling pathway. The hypothesis is that ARC serves as a neuroprotectant in experimental stroke. In primary neuronal cultures, the ARC protein levels were significantly reduced after oxygen glucose deprivation (OGD). This observation was further corroborated by the fact that a) downregulation of the ARC protein by RNA-interference resulted in higher susceptibility to OGD and b) the introduction of recombinant TAT-ARC protein revealed a dose-dependent neuroprotective effect. Immunohistochemical analysis of mouse brains after focal cerebral ischemia displayed marked loss of ARC positive neurons at early time points after damage. Therefore we exploited the TAT-mediated delivery approach to compare the neuroprotective effect of the native ARC protein as well as for the non-degradable TAT-ARC K3R, 149D and the non-functional CARD domain mutant TAT-ARC L31F, G69R. In the in vivo model, mice were subjected to transient middle cerebral artery occlusion (MCAO). During MCAO, the TAT-proteins were stereotactically applied into the contralateral ventricle. The infarct sizes, measured using magnetic resonance tomography, showed a marked reduction in lesion size with TAT-ARC in comparison to TAT-β-galactosidase as control. Consistent results were obtained with the behavioral analysis (rotarod and pole test). In summary, TAT-mediated delivery of the ARC-protein improves the outcome after hypoxic damage in vitro and in vivo and thus is a promising candidate for molecular therapy in stroke.

Stephanie Miceli, A. Schreiter, D. Labuz, M. Schmelz, and H. Machelska

P10 Prevention of opioid peptide degradation for analgesia in inflamed peripheral tissue

Anaesthesiologie, Charité – Universitätsmedizin Berlin, CBF; Universitätsklinikum und Fakultät für Klinische Medizin Mannheim, Universität Heidelberg

During the course of inflammation, circulating immune cells are recruited to the damaged tissue where they release opioid peptides such as beta-endorphin and enkephalins. Secreted opioids can bind their receptors located on peripheral terminals of sensory neurons decreasing neuronal excitability and consequently reducing pain (Stein et al., Nat Med, 2003). Two membrane metallopeptidases, neutral endopeptidase (NEP) and aminopeptidase N (APN) are involved in the degradation of opioid peptides, mainly the enkephalins (Roques, Neurochem Res, 1996). The goal of the present study was to investigate the prevention of opioid peptide catabolism by inhibiting NEP and APN to elevate opioid levels and decrease pain in the inflamed tissue. In a model of unilateral hindpaw inflammation (Freund's adjuvant), we observed co-expression of beta-endorphin or Met-enkephalin with NEP or APN in immune cells accumulating in inflamed tissue. Injection of NEP and APN inhibitors into inflamed paws produced local analgesia, assessed with the paw pressure test. Using in vivo microdialysis, we could associate this analgesia to elevated extracellular enkephalin levels. Our results suggest that inhibition of NEP and APN on immune cells prevents the degradation of their released enkephalins and this elevated peptide level consequently leads to analgesia in the inflamed tissue. Inhibiting the enzymatic degradation of endogenous opioids offers a promising strategy for pain control without adverse centrally-mediated side effects.

Ismini E. Papageorgiou, S. Gabriel, O. Kann, and U. Heinemann

Redistribution of glutamine synthetase in temporal lobe epilepsy: evidence from the rat pilocarpine model

P11

Institute of Neurophysiology, Charité – Universitätsmedizin Berlin

Glutamine synthetase (GS) is an astrocytic enzyme, which catalyzes the synthesis of glutamine from glutamate and ammonia. In the central neural system GS has a mutual role as nitrogen detoxifying agent and glutamate shuttle mechanism. GS expression and enzymatic activity is reported to be reduced in the hippocampus of patients with temporal lobe epilepsy (TLE). Glutamate accumulation and excitotoxicity has been hence attributed to its insufficient detoxification. Quantification of altered GS expression in epilepsy by means of morphology and biochemical methods has been only semi-quantitative up to present.

Aim, Methods In this study we sought to characterize GS expression in the hippocampus of rat pilocarpine-induced model of TLE using stereological and morphometrical analysis.

Results Our results suggest GS redistribution rather than downregulation. Neither the number of GS expressing astrocytes nor the total process volume was found altered for different hippocampal subregions of chronic epileptic rats compared to controls. A significant shift of GS expression from distal to proximal, thicker processes was the hallmark of epileptic rats. Moreover, GS displayed significantly altered astrocyte – vessel relationship with selective perivascular GS accumulation.

Conclusion GS in the rat pilocarpine model of TLE was rearranged rather than downregulated. The epileptic hippocampus was characterized by redistribution of the enzyme from distal to proximal astrocytic branches and perivascular sequestration of GS-expressing astrocytes with tendency to attach on vascular walls.

Future Directions The contribution of GS vessel affinity to excitotoxicity in epilepsy remains to be functionally elucidated.

Julia Parnis,[1] I. Sekler,[2] N. Freyer,[1] H. Kettenmann,[1] and C. Nolte[1]

P12 The physiological role of mitochondrial Na^+/Ca^{2+} exchanger NCLX for microglial Ca^{2+} homeostasis

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Calcium (Ca^{2+}) signaling via metabotropic receptors can affect many functions of microglial cells. Metabotropic receptor activation triggers the release of Ca^{2+} from the endoplasmic reticulum (ER) and the depletion of the ER Ca^{2+} stores results in the activation of store-operated Ca^{2+} channels (SOC). Mitochondria are important Ca^{2+} buffers and influence the time course and amplitude of the Ca^{2+} response. The Na^+/Ca^{2+} exchanger NCLX has been identified as an important route for the efflux of Ca^{2+} from the mitochondria (Palty, R. et al., 2010). We have now studied the expression and significance of NCLX in microglia. We found enrichment of NCLX in mitochondrial fractions obtained from cultured primary microglia. We could demonstrate that NCLX activity affects microglial Ca^{2+} responses: inhibition of NCLX by the specific blocker, CGP37157, resulted in a marked reduction of the Ca^{2+} response triggered by metabotropic agonist complement factor 5a. This reduction was mainly due to the shortening of the response.

To activate SOC we applied thapsigargin or ATP. We observed a significant reduction of SOC entry in the presence of the blocker. We also tested the impact of NCLX on migration and release activity. Pre-incubation of cells with CGP37157 attenuated ATP-triggered migration and LPS-triggered IL-6 release, but not TNFa release. In conclusion, our results indicate that in microglia NCLX is expressed in the mitochondria, and its activity influences microglial functions.

Muhammad Liaquat Raza,* A. Maslarova, and U. Heinemann

Anticonvulsant actions of sK-channel enhancer

P13

Institute of Neurophysiology, Charite – Universitätsmedizin Berlin

Small conductance calcium-activated potassium channel (sK-channel) belongs to a family of Ca^{2+}-activated K^+ channel and plays an important role in regulation of neuronal excitability. Activation of sK channel results in the hyperpolarisation of membrane resulting in the reduction of excitability, thus may have an anticonvulsant action. In the present study we have evaluated the anticonvulsant action of sK-channel enhancer by inducing seizure-like events (SLEs) in acute hippocampal slices of rat. SLEs were induced by 4-aminopyridine. Once the SLEs were stabile, CyPPA (sK-channel enhancer) was tested at doses of 50 µM and 100 µM. Electrophysiological recording was performed in an interface setup. CyPPA at dose of 50 µM didn't block SLE, rather delayed the interval between SLEs, whereas at the dose of 100 µM SLE were completely blocked. Based on these findings we suggest that sK-enhancer plays a role in reducing membrane hyperexcitability and thus may have potential to be an anticonvulsant agent.

Clemens Reiffurth, M. Alam, M. Zahedi-Khorasani, and J. P. Dreier

P14 Catalytic isoforms of the Na,K-ATPase differentially modulate the threshold for spreading depolarizations in mice

Center for Stroke Research, Experimental Neurology, Charité – Universitätsmedizin Berlin

Mutations in ATP1A2, the gene encoding the Na,K-ATPase alpha2 subunit, have been identified in patients suffering from a severe form of migraine with aura: familial hemiplegic migraine type 2 (FHM2). It has been hypothesized that spreading depolarization (SD, spreading depression), the neurophysiological process underlying migraine aura, might be facilitated by a loss of function of a single allele of the gene encoding the alpha2 subunit. To investigate the consequences of a deficiency in Na,K-ATPase alpha isoforms we employed heterozygous knockout mice lacking one copy of the alpha2 subunit (alpha2+/-) encoding allele. In acute brain slices, SD was triggered focally by droplet application of 1 M KCl solution, by electrical stimulation or by stepwise increasing the K^+ concentration in the bathing solution. We recorded changes in extracellular K^+ concentration, the accompanying slow extracellular potential shift, as well as changes in intrinsic optical signals to assess spatiotemporal patterns. To further investigate whether the observed effects were specific for a reduced amount of the alpha2 isoform, alpha1 and alpha3 heterozygous (alpha1+/- and alpha3+/-) mice were included in this study. We found a significantly lowered ($P < 0.001$) threshold concentration for K^+ to trigger SD in alpha2+/- mice compared to wild-type mice. This fact was reflected by a 22% shortening of the wash-in time needed to induce SD. No significant reduction in threshold concentration was found in alpha1+/- or alpha3+/- mice compared to their wild-type littermates indicating that the observed effect in the alpha2 group is specific for this isoform. These results bolster the notion that different catalytic Na,K-ATPase alpha isoforms have distinct functional properties and substantiates the hypothesis that functional haploinsuffiency may underlie the increased susceptibility to SD in FHM2.

Christine Römer, C. Meisel, and A. Meisel

The role of central nervous system injury induced immunodeficiency (CIDS) in protection from autoaggressive immune responses following middle cerebral artery occlusion (MCAo) in 2d2 transgenic mice

P15

Department of Experimental Neurology, Charité – Universitätsmedizin Berlin

Central nervous system (CNS) injury, such as stroke, leads to immunodeficiency (CIDS). Routes by which CNS modulates immune system include sympathetic nervous system (SNS), hypothalamic-pituitary-adrenal axis, and vagus nerve. According to our hypothesis, CIDS help to protect organism from autoaggressive immune responses (AIRs). Here, we aim at elucidating the role for SNS-mediated immunodepression in protection against AIRs after stroke.

We use 2d2 transgenic mice that carry a T cell receptor for mouse myelin oligodendrocyte glycoprotein (mMOG35-55). Stroke is induced by middle cerebral artery occlusion (MCAo) lasting 60 minutes. Enrofloxacin (5 mg/kg) is administered preventively until 7 days after MCAo to rule out infections. SNS activity is blocked by administration of propranolol (30 mg/kg) immediately before, as well as 4 and 8 hours after MCAo. Infiltration of transgenic T cells to brain is assessed by flow cytometry. The functionality of T cells is evaluated by enzyme-linked immuno spot (Elispot) assay and flow cytometry. Development of experimental autoimmune encephalomyelitis (EAE) like symptoms is monitored by applying EAE-like symptom score from day 7 until day 13 following MCAo.

Results from our pilot study show no differences in the number and ratio of brain infiltrating immune cells among propranolol- and saline-treated animals. Surprisingly, transgenic T cells from the spleens of propranolol-treated mice were less reactive to MOG peptide in terms of interferon-gamma (IFN-γ) and inteleukin-4 (IL-4) production ($p < 0.05$ and $p < 0.01$, respectively) when compared with controls. No differences in EAE-like symptoms were observed between the groups.

Further studies with larger groups are needed to investigate whether the findings from this pilot study are reproducible and to verify the role for SNS axis of CIDS against AIRs.

Clarisse Roth, M. Busch-Dienstfertig, and C. Stein

P16 The inverse response of mu-opioid receptor activation in the naked mole-rat

Forschungslabor der Klinik für Anästhesiologie, Charité Campus Benjamin Franklin; Leibniz-Institut für Zoo und Wildtierforschung (IZW) im Forschungsverbund Berlin (Hofer and Hildebrandt)

Mutations in ATP1A2, the gene encoding the Na,K-ATPase alpha2 subunit, have been identified in patients suffering from a severe form of migraine with aura: familial hemiplegic migraine type 2 (FHM2). It has been hypothesized that spreading depolarization (SD, spreading depression), the neurophysiological process underlying migraine aura, might be facilitated by a loss of function of a single allele of the gene encoding the alpha2 subunit. To investigate the consequences of a deficiency in Na,K-ATPase alpha isoforms we employed heterozygous knockout mice lacking one copy of the alpha2 subunit (alpha2+/-) encoding allele. In acute brain slices, SD was triggered focally by droplet application of 1 M KCl solution, by electrical stimulation or by stepwise increasing the K^+ concentration in the bathing solution. We recorded changes in extracellular K^+ concentration, the accompanying slow extracellular potential shift, as well as changes in intrinsic optical signals to assess spatiotemporal patterns. To further investigate whether the observed effects were specific for a reduced amount of the alpha2 isoform, alpha1 and alpha3 heterozygous (alpha1+/- and alpha3+/-) mice were included in this study. We found a significantly lowered ($P < 0.001$) threshold concentration for K^+ to trigger SD in alpha2+/- mice compared to wild-type mice. This fact was reflected by a 22% shortening of the wash-in time needed to induce SD. No significant reduction in threshold concentration was found in alpha1+/- or alpha3+/- mice compared to their wild-type littermates indicating that the observed effect in the alpha2 group is specific for this isoform. These results bolster the notion that different catalytic Na,K-ATPase alpha isoforms have distinct functional properties and substantiates the hypothesis that functional haploinsuffiency may underlie the increased susceptibility to SD in FHM2.

Steffen B. Schulz, Z.-J. Klaft, A. R. Rösler, U. Heinemann, and Z. Gerevich

Endogenous ATP modulates gamma oscillations induced by ACh in the rat hippocampus differentially via P2X and P2Y receptors in vitro

P17

Institute of Neurophysiology, Charité – Universitätsmedizin Berlin

ATP is a well known energy supplier within cells and an extracellular signalling molecule released i.a. by neurons and glia. The present study was designed to investigate the role of ATP and its receptors on neuronal network activity. Gamma oscillations (30–90 Hz) were induced in the CA3 region of acute hippocampal slices of the rat by using either acetylcholine (ACh) or kainic acid (KA). ATP reduced the power of KA-induced gamma oscillations exclusively by the activation of adenosine receptors after its degradation. In contrast, ACh-induced oscillations were reduced by both adenosine and ATP receptors: the adenosine and P2 receptor component of the inhibition by ATP comprised ~55% and ~45%, respectively. This modulation also occurred by endogenous ATP since inhibition of the degradation of ATP had an inhibitory effect. By means of more specific antagonists it could be revealed that ionotropic P2X1-3 receptors inhibited ACh-induced gamma power whereas the metabotropic P2Y1 receptor increased it. We measured the level of extracellular ATP in different layers of the CA3 region during the development of oscillations by using ATP-sensitive electrochemical biosensors. We found that the concentration of ATP declined by ~0.6 µM during the generation of ACh-induced gamma oscillations exclusively in the pyramidal cell layer whereas the concentration of ATP did not change during KA-induced gamma oscillations. In conclusion, our results suggest that endogenously released ATP finely modulates the power of cholinergically induced gamma oscillations in the CA3 region of the hippocampus by activating, besides adenosine receptors, P2X and P2Y receptors.

Katyayni Vinnakota,[1] D. S. Markovic,[1, 2] R. Glass,[1] and H. Kettenmann[1]

P18 Minocycline attenuates the microglia-assisted glioma expansion and invasion

1 Department of Cellular Neurosciences, Max Delbrück Center for Molecular Medicine Berlin-Buch; 2 Department of Neurosurgery, Helios Klinikum Berlin-Buch

Gliomas are most common brain tumors arising in humans. The hallmark of malignant gliomas is invasion into the brain parenchyma, which limits the efficacy of conventional therapies. Invasion is facilitated by metalloprotease enzymes that degrade the extracellular matrix. These are released as pro-forms and get activated upon cleavage by membrane-bound metalloproteases. We have previously reported that membrane type 1 metalloprotease (MT1-MMP) is upregulated in glioma-associated microglia. Soluble factor(s) released from glioma cells trigger the expression and activity of MT1-MMP via Toll-like Receptor (TLR) signaling and activation of p38 MAPK (Markovic, D., et al 2009). The microglial MT1-MMP then activates glioma-derived pro-MMP2 and promotes glioma diffusion. Currently, we are investigating the role of minocycline, a second-generation tetracycline antibiotic, on microglia-assisted invasion of glioma into healthy brain using in vitro and in vivo tools. Our data so far indicate that minocycline, a reported blocker of p38 MAPK and microglia cell activation, interferes with MT1-MMP activity and expression at the mRNA and protein levels in primary microglia exposed to glioma conditioned medium. In organotypic brain slices inoculated with glioma tumor, minocycline induced a significant decrease in tumor expansion, with no effect on microglia-depleted slices. Also, a reduction in tumor size was noticed in an experimental glioma mouse model upon minocycline administration, alongwith a decrease in MT1-MMP expression upon immunostaining. Our results indicate that minocycline could be a potential candidate to existing glioma therapies.

Marietta Zille, I. Przesdzing, H. Klawitter, U. Dirnagl, and A. Wunder

Characterization of cell death in primary neuronal and glial cells after Oxygen-Glucose Deprivation (OGD) by flow cytometry

P19

Center for Stroke Research Berlin; Experimental Neurology, Charité – Universitätsmedizin Berlin

To monitor stroke-induced brain damage, non-invasive imaging techniques using specific cell death markers are highly desirable. Specificity of non-invasive imaging signals after injection of candidate markers is usually assessed by manual counting of cells stained with different cell death markers in tissue sections, which is time-consuming and limited by low cell numbers. In this study, we investigated if flow cytometry is an alternative because the entire cell population and multiple markers can be evaluated.

We characterized primary cortical neuronal cultures regarding their β-III-tubulin and glial fibrillary acidic protein (GFAP) immunoreactivity. Therefore, a protocol for the detachment of primary cortical neuronal cells was established. Primary cortical astrocytes were added to the neuronal cultures, which then underwent OGD. Damage was assessed using different cell death markers using flow cytometry as well lactate dehydrogenase (LDH) release.

We could detect a decrease of the fraction of β-III-tubulin-positive cells over time, whereas the percentage of GFAP-positive cells increased. When we added astrocytes to the cultures prior to OGD, the LDH release was significantly reduced in a dose-dependent manner. Cells positive for annexin V and TUNEL could be detected after OGD.

We conclude that flow cytometry might be used as an alternative to manual counting for the analysis of brain cells in a high-throughput manner. Primary neurons and astrocytes can be specifically and reliably characterized, regarding cell type and markers for cell death. It remains to be shown whether brain tissue after experimental stroke can be separated and analyzed by using flow cytometry.

Daniel Beis, V. Mosienko, E. Popova, F. Qadri, M. Bader, and N. Alenina

P20 Depression, anxiety and serotonin: Phenotyping Tph2-deficient animals

Max Delbrück Center for Molecular Medicine Berlin-Buch

Depression and anxiety-disorders are dispersing mental dysfunctions that bear relative high life time prevalence in western countries (12%–20%). Clinical evidence indicates a broad involvement of serotonin (5-HT) in several mental diseases. The enzyme tryptophan hydroxylase 2 (TPH2) is a rate limiting enzyme in serotonin synthesis in the central nervous system (Walther et al., 2003).

We created a Tph2-deficient mouse model (Tph2-/-) which lacks 99% of brain 5-HT. Tph2-/- mice display slight changes in cardiovascular parameters, but no disruption of brain anatomy or severe stereotypes are visible in these animals (Alenina et al., 2009).

To investigate the influence of 5-HT and its receptor subsystems on the expression of depressive and anxiety-like phenotypes we analyzed affective behavior in more detail in Tph2-deficient mice.

To overcome the limits of the mouse-model and for a deeper insight into the species specific traits in serotonergic phenotypes we are also creating a Tph2-knockout rat using a new Zinc-Finger-Nucleases technology.

Valentina Mosienko, M. Todiras, R. Plehm, M. Bader, and N. Alenina

Sleep regulation and circadian rhythms in mice lacking central serotonin

P21

Max Delbrück Center for Molecular Medicine Berlin-Buch

Biosynthesis of serotonin in the brain and in the peripheral system is limited on the first step by two distinct tryptophan hydroxylase enzymes, TPH2 and TPH1 respectively. Recently, by genetically ablating Tph2 we generated mice lacking serotonin in the central nervous system (Tph2-/-, Tph2-deficient mice).

Serotonin is extensively entangled in fundamental aspects of sleep and circadian rhythms regulation. Using Tph2-deficient mice as a model with altered brain serotonin we assessed the role of the serotonergic system in the regulation of sleep and adaptation of circadian rhythms of blood pressure (BP), heart rate (HR), and locomotor activity (LA) to light cycle shifts. The parameters were measured for 3 days under basal conditions (6 am – 6 pm light phase; 6 pm – 6 am dark phase), followed by 7 days of inverted light (6 pm – 6 am light phase; 6 am – 6 pm dark phase) and 7 days of free run (24 hr darkness).

Using electroencephalogram and electromyogram recordings we detected in Tph2-deficient mice under normal dark-light conditions a trend towards increased slow wave sleep at the late evening, whereas wild-type (WT) animals stay in active awake during this period. Moreover, using radiotelemetry we detected a 2 hr shift in acrophase for LA and BP under baseline condition in Tph2-deficient mice in comparison with WT animals.

Under the reversed light condition Tph2-deficient mice can easily adapt to changed light, showing the same acrophases for BP, LA, and HR as WT mice.

However, in free-running conditions Tph2-/- mice lose the sleep-wake rhythms after 4 days, staying awake episodically during 24 hr.

Our findings suggest an important role for central serotonin signaling in sleep control and adaptation processes.

Kristin Stock,[1] M. Synowitz,[1, 2] H. Kettenmann,[1] and R. Glass[1]

P22 Bone Morphogenetic Protein-7 release from endogenous neural precursor cells (NPCs) attenuates self-renewal of glioma stem cells but not of untransformed NPCs

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We previously reported that endogenous neural precursor cells (NPCs) are attracted to experimental brain tumors (glioma) in large numbers and reduce tumor size. Endogenous NPCs perform an anti-tumor response by specifically targeting CD133+ glioma cells with stem-like properties (GSCs) which control tumor growth and recurrence. Using an in vivo model we showed that glioma-associated PSA-NCAM+ NPCs express BMP7, but not BMP2 or BMP4. BMP7 is also the pre-dominant BMP in neurosphere cultures and is preponderantly expressed by PSA-NCAM+ NPCs, but not by differentiating NPCs or tumor cells. Moreover, BMP7 is constitutively released from neurospheres and induces canonical BMP signaling in GSCs. Exposure of GSCs to neurosphere-derived BMP7 induces GSC differentiation, attenuates GSC-marker expression, GSC self-renewal and the ability for tumor initiation. NPC-derived BMP or recombinant BMP7 reduces glioma expansion from GSCs by down-regulating the transcription factor Olig2 (Chirasani et al., 2010, Brain).

In this study, we investigated whether the BMP7-signaling also has a role in the physiological context. We applied the selective BMPR-I antagonist compound C to inhibit an auto- or paracrine effect in the culture. We measured overall expansion of endogenous NPCs by seeding the cells in clonal density and measuring sphere size and number. Furthermore, the proliferation- as well as cell death-rate of NPCs was analyzed. We found that none of these parameters was affected by compound C suggesting that the effect of BMP7 is restricted to the pathophysiological situation of a brain tumor.

Grietje Tessmann, V. Matyash, K. Färber, and H. Kettenmann

Serotonin modulates microglial phagocytosis and motility

P23

Max Delbrück Center for Molecular Medicine Berlin-Buch

Microglia, the brain macrophages, represent the immune cells of the brain. During any insult they transform from a ramified to an ameboid cell, can migrate to the site of injury and can release both neuroprotective as well as proinflammatory substances. It was shown that microglial cells express neurotransmitter receptors for GABA, norepinephrine and dopamine whose activation modulates microglial functions (Kettenmann and Pocock, 2007). Here we studied the impact of serotonin on microglial phagocytosis and motility. To quantify phagocytosis activity, we determined the uptake of serum coated latex beads, in cultured microglia from newborn NMRI animals, in acute brain slice preparations from 6–9 day old mice and from 8 weeks old adult NMRI mice. Application of 1 µM, 10 µM, 100 µM and 1 mM serotonin reduced significantly phagocytosis activity in primary microglia to 88% ± 9%, 82% ± 8%, 81% ± 9% and 85% ± 10% respectively (SEM, n ≥ 5). In comparison we tested also acutely isolated brain slices as an in situ model to study microglia in their tissue environment. 1mM Serotonin stimulation resulted in a decrease of phagocytosis activity to 76% ± 7% (SEM, n = 5) in slices taken from p 6–9 old animals whereas in slices of adult mice we did not observe any significant change in phagocytosis activity (n = 6). In a second set of experiments we tested the impact of serotonin on the microglial response to an insult caused by a laser lesion. We determined and quantified the movement of processes to the lesion in acute slices from CX_3CR_1-EGFP mice. Concentrations of 100 µM and 1 mM serotonin caused an increase in the response of microglial processes toward the laser lesion. Stimulation with 10 µM serotonin did not show any significant effect. These data indicate that microglial cells express functional serotonin receptors which control microglial executive functions.

José R. Donoso, N. Maier, D. Schmitz, and R. Kempter

P24 Reliability of synaptic conductance measurements during sharp-wave ripples

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During slow-wave sleep or immobile resting periods, sharp wave-ripple (SPW-R) events can be measured in the LFP of the CA1 region of the hippocampus of rodents. The basic mechanisms of how SPW-R are initiated, maintained and terminated are unknown.

Information about inhibitory and excitatory currents received by a CA1 cell during a SPW-R would allow us to constrain parameters in network models aiming to elucidate the mechanisms for the generation of this oscillatory pattern.

To quantify the time course of excitation and inhibition, patch clamp methods measure the synaptic input that a neuron experiences within the network. Current traces obtained at two different holding potentials are mathematically combined in order to disentangle the excitatory and inhibitory components. The precise alignment of intracellular currents required by this method is particularly difficult in SPW-R data.

In order to assess the reliability of the computational extraction of synaptic quantities in the context of SPW-R, we defined a synaptic phase space where two orthogonal axes represent the value of excitatory and inhibitory conductances, respectively. In this space, the time course of synaptic conductances is depicted as a trajectory. To obtain a consistent estimation of conductances, it is essential to make sure that the traces combined correspond to a common trajectory. By means of a single compartment cell model, we illustrate the difficulties in ensuring this fundamental requirement. In addition to the rich variability in terms of frequency, phase and amplitude exhibited by SPW-R, we show that the phase structure of the current measured is altered by the value of the holding potential used.

We conclude that careful selection of holding voltages during current measurement can improve reliability of identification. However, it is essential to count on a characterisation of SPW-R that exhibits a cluster structure in some feature space.

Kai Görgen,[1] C. Reverberi,*,[1] and J.-D. Haynes*,[1,2]

Decoding neural representations of rules and rule order

P25

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Conditional rules of the form "if x then y" are of vital importance for everyday life. Recently, researchers started to investigate the neural substrate underlying rule processing. A critical aspect of rule processing that has been neglected so far is that many situations require rules to be executed in a specific order. For example, it might be wise to apply the rule "If you don't have money, go to the ATM" *before* the rule "If you want ice-cream, go to the ice-cream shop".

Here, we present results of an fMRI study in which we successfully decoded the identity of two simultaneously active rules as well as their application order from local patterns of fMRI data using multivariate pattern classifiers.

Representations of rule identity and rule order were found in bilateral supero-lateral parietal cortices and right ACC. Additional representations of rule identity (but not order) were found in right dorso-lateral prefrontal cortex (dlPFC). In ACC, regions containing representations of rules and rule order overlapped. In contrast, dissociations between both regions were found in supero-lateral parietal cortices and lateral PFC.

The locations of rule representations fit well with recent findings by Reverberi & Haynes (in prep). The found dissociations between regions containing rule and rule order suggest that both features of rule processing are handled in different ways by the brain.

In conclusion, we successfully localized representations of two defining features of complex rule sets, rule identity and rule order. Additionally, our results provide evidence that the brain treats both types of information differently.

Kerstin Hackmack, M. Weygandt, C. Pfüller, J. Bellmann-Strobl, F. Paul, and J.-D. Haynes

P26 Predicting clinical disability in multiple sclerosis based on structural MRI

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The association between brain magnetic resonance (MR) images and clinical disability in patients suffering from Multiple Sclerosis (MS) is generally weak and known as clinico-radiological paradox. In the present study, we explored the usefulness of pattern recognition methods in predicting the following markers of symptom severity: Disease duration, 9-Hole Peg Test (9-HPT), Timed 25-Foot Walk Test (TWT), Paced Auditory Serial Addition Task (PASAT) and Expanded Disability Status Scale (EDSS).

For this purpose, we extracted local brain tissue intensity patterns from structural T1 and T2 weighted MR images of forty MS patients (relapsing-remitting type) and conducted a canonical correlation analysis for each of the markers. After performing a leave-one-out cross-validation, the result is given by the correlation between predicted and true clinical scores for each position in the brain.

Different regions encoding symptom severity have been found for T1 and T2 weighted images and included white as well as grey matter regions. Disease duration could be significantly predicted from somatosensory cortex and posterior parietal cortex. Motor disability as measured by 9-HPT and TWT could be decoded from motor areas such as cerebellum, primary motor cortex, and posterior parietal cortex. The PASAT score could be decoded from working memory areas, e.g. angular gyrus, prefrontal cortex, and superior parietal lobe. For EDSS, frontal areas have been found.

These findings suggest that local intensity patterns are clinically relevant biomarkers of clinical disability in MS and should be considered in future studies.

Jorge Jaramillo,*[1,2] R. Schmidt,[1,2] and R. Kempter[1,2]

A model for inheritance of hippocampal phase precession: From CA3 to CA1

P27

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Hippocampal place cells exhibit phase precession, the advancement of a neuron's firing phase with respect to theta oscillations (4–12 Hz) in the local field potential. Phase precession has been observed in the CA1 and CA3 regions of the hippocampus during exploratory behavior and its functional role has been linked to memory and spatial navigation. An open question is the origin of the phase precession observed in the CA1 region. Previous models of phase precession have assumed that phase precession is generated intrinsically in the CA1 region. However, here we investigate the possibility of the CA1 region inheriting phase precession from the CA3 region through computational modeling. The model of inheritance consists of a feedforward input from a subset of the CA3 place cell population onto the CA1 region via the Schaffer Collaterals (SC). Taking into account the firing rate within the place field and the parameters characterizing excitatory postsynaptic potentials (EPSPs) along the SC, we are able to simulate the membrane potential and calculate its analytical form as a function of the model parameters. The resulting membrane potential trace is similar to recent experimental recordings (Harvey et al. [2009]), suggesting that CA1 can inherit phase precession from CA3. Furthermore, we analyze how a signal-to-noise ratio analysis constrains the parameters of the model, particularly on the minimal amount of neuronal input necessary.

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P28 Alzheimer's disease and gene regulation: A possible role of Aβ in the nucleus

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Background The pathogenic effects observed in AD are ascribed to soluble low-n oligomers of Aβ42. Recently, we could show that cellular toxicity and LTP inhibition of Aβ is not a simple cause of oligomerization but a consequence of a specific Aβ-conformation determined by the GxxxG interaction motif. Aβ42 peptides with an alanine substitution of glycine (G33A) were much less toxic than Aβ42wt. Our findings unraveled that G33 is the key amino acid determining cellular activities of Aβ. In the present study we have discovered a novel role for Aβ42 in nuclear signaling. The observed involvement of the peptide in gene regulation was specific for Aβ42 and could either represent a normal or a gain-of-function.
Methods Neuroblastoma cells were treated with synthetic Aβ peptides. The internalization was monitored by ELISA, LSM and EM. Using ChIP technique we could demonstrate that Aβ specifically binds either directly or indirectly to promoters. To verify the functional binding of Aβ peptides to chromatin we investigated the mRNA levels by qRT-PCR.
Results Different forms of Aβ were rapidly internalized and transported within the cell from the cytoplasm into the nucleus. There, Aβ peptides accumulated in a time dependent manner. Only the accumulation of Aβ42 led to changes in the expression of various mRNAs. Whereas the wild-type sequence affected mRNA expression levels the Aβ42G33A peptide did not, underlining the importance of G33 for the nuclear signaling function of Aβ42.
Conclusion We conclude that Aβ42 has a specific transcriptional regulatory function. Our data imply that deregulation of Aβ target genes could be an alternative pathway for Aβ-induced neurotoxicity.

Gürsel Çalışkan and U. Heinemann

Effects of corticosterone on hippocampal gamma oscillations in vitro

P29

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Acute stress triggers the release of variable amount of steroid hormones, such as corticosterone (CORT), which alters neuronal functions in a time-dependent manner. CORT can bind to high affinity mineralocorticoid receptors (MR), which are mainly expressed in limbic regions, or to low affinity glucocorticoid receptors (GR) which have a broader distribution in the brain. Increase of corticosteroid hormones to high levels have been shown to interfere with hippocampus-dependent memory formation. Moreover, recent studies provide evidence that CORT has opposite effects on synaptic plasticity in ventral versus dorsal hippocampus, but very little is known about the impact of stress hormones on hippocampal oscillations, which have been implicated in the formation and consolidation of declarative and spatial memory. We examined the effects of CORT on gamma oscillations using 3 different in vitro models: 1) 10 µM ACh co-applied with 2 µM ACh esterase inhibitor physostigmine, 2) Kainate (100 nM) or 3) Carbachol (CCh) (20 µM) in the CA3 ventral hippocampal rat slices. High concentration of CORT (1µM), which activates both GR and MR, resulted in decrease in power of Kainate- and CCh-induced gamma oscillations (51 +/- 1% and 85 +/- 4%, of control, respectively) whereas ACh-induced oscillations were not affected (103 +/- 7%). Low concentrations of CORT (30 nM), which activates only MR, did not have any major effect on in vitro gamma oscillations. Application of GR agonist, dexamethasone (100 nM), resulted in 79 +/- 27% increase in the power of ACh-induced gamma oscillations. These data suggest that different types of in vitro gamma oscillations are affected differently by CORT (1 µM) which indicates involvement of different types of interneurons in generation of gamma oscillations. Furthermore, GR activation seems to be involved in modulation of in vitro gamma oscillations.

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P30 The let-7 miRNA as central regulator of stem cell commitment

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miRNAs are small, non-coding RNAs with a global influence on the proteome. miRNAs regulate fundamental processes such as early development, cell specification, growth control and apoptosis, but also higher order functions in the CNS such as synaptic plasticity and memory formation. We are studying the role of the let-7 miRNA, a crucial regulator of stem cell self-renewal and neural commitment.

Let-7 regulates two novel pluripotency genes, Lin28 and Lin41. We recently assigned molecular functions both to Lin28 and Lin41, first defining Lin28 as a let-7 specific RNA binding protein that inhibits functional maturation of let-7 by the Dicer ribonuclease. These results provide a mechanistic understanding of the oncogenic activity of Lin28 and the ability of Lin28 to promote pluripotency in somatic cells. Lin41 is a Trim family E3 ubiquitin ligase and the founding member of the Trim-NHL subfamily of developmental regulators. Lin41 interacts with and ubiquitinates the essential miRNA pathway protein Ago2 and is therefore a repressor of miRNA-mediated silencing. Lin28 and Lin41 cooperate in suppressing the neurogenic miRNA let-7. Inactivation of Lin41 in gene trap mice results in defective neural tube closure, a phenotype currently under study in our lab. We are generating a conditional allele, to allow functional analysis of Lin41 in adult neurogenic zones.

Benjamin Wagner,[1] M. Voss,[1] B. Schott,[1, 2] and J. Behr[1, 3]

Encoding of novel information in schizophrenia – an fMRI study

P31

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Novel events in the environment tend to attract attention and seem to be efficiently incorporated into the long-term memory system. Encoding of novel information has been proposed to rely on the time-locked release of dopamine in the hippocampal formation during novelty detection originating from neurons in dopaminergic midbrain structures, i.e. substantia nigra (SN) and ventral tegmental area (VTA). The integrity of this functional mesolimbic loop between midbrain and the hippocampus (HC) seems to be crucial for incorporating these novelty-related signals into long-term memory depending on their behavioral relevance. Dopaminergic modulation is known to play a key role in executing effective goal-directed behavior. For schizophrenia, the dopamine-hypothesis states that a disinhibited mesolimbic dopamine system may lead to psychotic symptoms such as hallucinations and delusions. An alteration of the HC-VTA-loop may be one key factor contributing to the dopamine-excess in schizophrenic patients. Therefore, it seems highly plausible that such a stimulus- independent release of dopamine could interfere with the detection and processing of novelty per se, leading to cognitive impairment due to insufficient memory-encoding. Furthermore, as recently proposed, excessive dopamine-release may lead to abnormal salience attribution.

In this clinical study we use functional magnetic resonance imaging (fMRI) to investigate how dysfunction of the mesolimbic loop between midbrain and HC in a population of unmedicated patients suffering from schizophrenia may lead to abnormal encoding of novel information and subsequent memory impairment.

Christoph Korn,[1, 2] K. Prehn,[3] H. Walter,[2, 4] and H. R. Heekeren[1, 2, 3]

P32 Positively biased processing of social feedback: A cognitive neuroscience approach

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Humans process self-related feedback in a positively biased way, i.e. they tend to accept desirable social feedback such as praise uncritically while they receive undesirable social feedback such as blame with mistrust. This is supposed to be an important mechanism by which humans maintain and enhance their self-esteem (Taylor & Brown, 1989). Recently, preferential updating for desirable versus undesirable information has been characterised for optimism (Sharot, Korn & Dolan, in prep.). However, the mechanisms regarding self-related social feedback are still unclear. In our fMRI design we manipulated desirable and undesirable social feedback quantitatively and measured the amount by which participants updated their beliefs. Briefly, in order to get to know each other, five participants played the board game "monopoly". Afterwards they rated each other on 80 trait adjectives (e.g. modest, arrogant). On the next day in the scanner, each participant first rated herself and then saw how the others had rated her. To assess how this feedback changed self-perception, participants rated themselves a second time outside the scanner. Behaviourally, if the others' rating was more desirable than expected participants changed their self-ratings and saw themselves in a more positive way. However, if the others' rating was less desirable than expected participants did not update their self-ratings. On the basis of previous studies fMRI on social learning (Behrens, Hunt & Rushworth, 2009) we expect that striatal and prefrontal cortex activity will correlate with differences between self-rating and feedback.

Milena Rabovsky, W. Sommer, and R. Abdel Rahman

"For to everyone who has, more shall be given": Semantic richness enhances implicit word learning

P33

Department of Psychology, Humboldt-Universität zu Berlin

Words differ considerably in the amount of associated semantic information. Despite the crucial role of meaning in language, it is still unclear whether and how this variability modulates language learning. Here, we provide initial evidence demonstrating that the amount of semantic features associated with a given word influences implicit learning in repetition priming. Electroencephalographic recordings were obtained while participants performed a visual lexical decision task; the complete stimulus set was repeated once. Repetition priming effects on performance accuracy and the N400 component of the event-related brain potential were enhanced for words with many semantic features. These findings suggest a driving impact of the richness of semantic representations on learning and plasticity within the lexical-conceptual system.

Anne Weigand, S. Grimm, F. Harlis, A. Mungee, P. Kazzer, M. Bajbouj

P34 Neural correlates of the emotional working memory – a neuronavigated rTMS study

Cluster of Excellence Languages of Emotion, Freie Universität Berlin; Department of Psychiatry, CBF, Charité – Universitätsmedizin Berlin

Many studies show the functional role of the prefrontal cortex in working memory. However, the specific brain areas involved in this memory system and its interaction with emotions remain still unclear. Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive method to modulate brain activity by inducing an electric current within neurons. The combination of functional magnetic resonance imaging (fMRI) and rTMS represents an innovative research approach to investigate causal brain-behavior relations in higher cognitive functions.

Fifteen healthy male volunteers aged between 18 and 28 years completed in three different sessions variants of the n-back task (2-back) with emotional stimuli (positive, negative and neutral words). In order to identify the individual stimulation point, the participants performed the task first in the fMRI scanner and the highest brain activity was measured in the left dorsolateral prefrontal cortex (DLPFC). In a randomized cross-over design, offline rTMS (10 Hz, 50 sec, 90% of the motor threshold) was delivered to the left DLPFC or to an occipital control region between task blocks. The reaction times and the accuracy were registered.

The results showed significant shorter reaction times after the high-frequency rTMS of the left DLPFC compared to the control condition. Remarkably, this effect could be attributed to words with positive emotional values. Regarding the accuracy, there was no significant difference between the experimental and control rTMS condition. In agreement with other studies, these findings support the essential role of the left DLPFC in working memory functions as well as the left hemispheric processing of positive emotions.

Marc Borner

Subpersonal conditions of self-consciousness

P35

Institute of Philosophy, Humboldt-Universität zu Berlin

One can take at least two different perspectives to describe our self-consciousness: a personal and a subpersonal one. In the former we are recognized as being persons in a social environment. The latter describes our biological base. This study will connect both levels to expend the phenomenon of prereflexive self-consciousness.

Philosophically prereflexive self-consciousness is a fundamental phenomenal property of any conscious being and is realized by a certain point of view with a specific subjective quality. It describes the fact that we are always, immediate and error-free aware that all mental acts are lastly experienced as being ours. In this it allows us a basic distinction of our own mental acts from other objects and creatures and thus forms a base for any more complex form of consciousness. German philosopher Manfred Frank provided the most thorough analysis here, stating that purely philosophical investigations to the notion of prereflexive self-consciousness have deemed the phenomenon to be not analyzable apart from circular approaches. My approach will try to expand the phenomenon in providing a philosophical analysis of its subpersonal conditions.

I will firstly try to show that the traditional philosophical theory is itself circular and secondly that prereflexive self-consciousness can be significantly expended via a philosophical analysis of Antonio Damasio's notion of core consciousness. Especially emotional processing and a non-language-based-memory including a first time framework seem crucial add-ons to the original philosophical theory. The method of applying a philosophical analysis of subpersonal data – as done in the example of prereflexive self-consciousness and core-consciousness – can also provide a broadening of existing philosophical theories of the mind in general and thus further the inter- and trans-disciplinary dialogue.

Katharina Grauel, K. Marter, and D. Eisenhardt

P36 Does reward magnitude effects associative strength and memory formation?

Freie Universität Berlin, Institut für Neurobiologie

In appetitive classical conditioning an animal learns that a previously neutral stimulus (conditioned stimulus, CS) is associated with a reward (unconditioned stimulus, US). After conditioning, the CS alone elicits a conditioned response (CR). The term associative strength describes the extent to which the CS predicts the reward. It is generally accepted that the associative strength is mirrored in the conditioned response during acquisition.

Repeated retrieval of a CS-US memory by the CS alone leads to a decreasing CR. This phenomenon is termed extinction and is caused by extinction learning; a process during which the animal learns that the CS is no longer associated with the reward (CS-noUS memory).

Recent data demonstrate a correlation between the US duration during appetitive classical conditioning and the stability of extinction memory visible 24 h after extinction with a CS alone. From this study we concluded that the stability of an extinction memory depends on the magnitude of the prediction error between the previously experienced reward during the CS-US association and the absence of the reward during memory retrieval (Stollhoff & Eisenhardt, 2009).

Nevertheless, it is unknown how the reward magnitude influences acquisition, a memory's stability and its biochemical identity in general. Therefore, we here test the impact of varying reward magnitudes (different US durations) on the conditioned response in single, restrained honeybees during acquisition and retrieval by recording and quantifying the activity of the honeybee's proboscis extending muscle M17.

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Analgesia and G protein activation exerted by novel opioid-neurotensin hybrid peptides

P37

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Opiates are the most widely used analgesics in the treatment of various pain states. However, they can produce a variety of secondary pharmacological side-effects, ranging from mild to life threatening. One of the solutions to these problems are chimeric compounds in which opioid pharmacophore is hybridized with other type of synergically active antinociceptive agent. Neurotensin (NT) is also a potent analgesic in animals but, unlike opiates, it doesn't induce such undesirable side-effects.

Importantly, activity and function of NT as well as its various analog compounds depend on their structures. In our previous studies we synthesized some new opioids-neurotensin hybrid peptides, considering the structure-activity relationship. Thus the C-terminal NT' fragment was modified by substitution of Arg8 and Arg9 by lysine residues that is known not to influence potency as well as substitution of Ile12 by Tle (tert-leucine) that should improves the metabolic stability, or D-Asp – in case of PK7. The endomorphin (the opioid pharmacophore) has been used as parent opioid sequence. However to improve its enzymatic stability and receptor affinity N-terminal Tyr1 has been replaced by 2,6, dimethyl-tyrosine (DMT) in one of the compound, whereas Pro2 has been replaced by D-lysine in all investigated opioids-neurotensin chimeras.

In the present study we would like to present PK7 and PK20 as active compounds with the ability to induce antinociception after central and peripheral administration and to activate G proteins.

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P38 A model in cancer pain treatment: Central and peripheral pain components

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It is common knowledge that classical opioids exert their strong antinociceptive effect mainly when acting on opioid receptors located in the central nervous system or the spinal cord. Nevertheless, the peripheral action of opioids must not be disregarded as a potential supporter therapy option. Such a peripherally acting drug might be beneficial in chronic pain treatment as shown in numerous animal models of inflammatory, neuropathic visceral pain and cancer pain. The major advantage is a possibility to treat pain symptoms with avoidance of minor side-effects, particularly tolerance occurring in morphine-treated patients. We examined the analgesic effect of a dimeric enkephalin analog-biphalin in a murine skin cancer pain model developed by an intraplantar inoculation of B16To melanoma cells. Animals developed robust thermal hypersensitivity in the tumor-bearing paw compared to saline-injected individuals. Biphalin produced a unilateral attenuation of thermal hyperalgesia in the tumor-bearing paw as assessed in the plantar test. The obtained results suggest a probable involvement of the peripheral opioid receptor-mediated analgesia. Apart from showing an antinociceptive effect in the periphery, biphalin also exerted a central antinociceptive effect as measured in the tail-flick test. Thus, biphalin, may become a useful drug in cancer pain treatment because it also shows low tolerance liability.

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Neurobiological tools to temporally and spatially interfere with protein synthesis

P39

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Photolabile protecting groups can be bound to functional groups of biomolecules to block their chemical and biological activity. The inactivated biomolecule ("caged compound") can be released by irradiation with short wavelength light, removing the protecting groups and restoring the molecule's bioactivity. This enables temporal precision and accurate delivery to a specific tissue of interest (spatial control).

We characterized new caged compounds that are important to study physiologic processes associated with translation, namely two inhibitors of protein synthesis (PSI), emetine and anisomycin. Both are frequently used in neuroscience to interfere with protein synthesis-dependent processes like long-term synaptic plasticity and memory consolidation.

The biological activity of the PSIs was masked with different protecting groups. The resulting caged compounds were photochemically characterized and their uncaging kinetic was analyzed in detail in an in vitro translation system. All caged compounds have high long-wavelength absorptions, good photorelease rates, are resistant to spontaneous hydrolysis in the dark and perform excellent in the in vitro translation assay. Our caged anisomycin has, compared to previous reports (Goard et al., Chem.&Biol. 2005 and Sadovski et al., Bioorg. Med. Chem. 2010), a higher solubility and can be used in lower concentrations.

Additionally, we tested our caged compound's applicability in HELA cells and in Drosophila transgenic flies.

These caged PSIs are efficient and reliable tools to probe the role of translation in a variety of neuroscientific applications and biological systems.

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P40 Optimal spatial periods of grid cells ensembles

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In 2004 grid cells in the medial entorhinal cortex have been found.[2] These cells have the remarkable property of assigning a hexagonal lattice to physical space, such that the neuron spikes whenever the rat moves through one of the lattice nodes. In order to encode space precisely, a population of grid cells is needed, to counteract the ambiguity introduced by the periodic firing fields of grid cells and to cover space.

We compute the resolution of grid codes in a realistic parameter regime, on a limited space with a finite amount of spiking cells and families of tuning curves for many different spatial period configurations. By resolution we refer to the mean square error of predicted position, defined as maximum likelihood estimate. This analysis reveals that there should be more small spatial periods than large periods present. This distribution largely resembles empirical observations by Brun et al.[1]

1 V Brun, T Solstad, K Kjelstrup, M Fyhn, M P Witter, E I Moser, M-B Moser. Progressive Increase in Grid Scale From Dorsal to Ventral Medial Entorhinal Cortex. Hippocampus, 1212: 2008.

2 M Fyhn, S Molden, M P Witter, E I Moser, and M-B Moser. Spatial representation in the entorhinal cortex. Science, 305 (5688): 2004

Dinah Nockemann, C. Stein, and P. A. Heppenstall

GIRK channel expression in peripheral sensory neurons differs between species

P41

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G protein coupled inward rectifying potassium channels (GIRK) control the excitability of neurons in response to activation of different G protein coupled receptors (GPCRs). Among those GPCRs are opioid receptors which can activate the GIRK channel by direct binding of the Gβγ subunit. Apart from activating GIRK channels, opioid receptors also inhibit voltage-gated Ca^{2+} channels. Interestingly, in peripheral sensory (dorsal root ganglion; DRG) neurons Ca^{2+} channel inhibition has been the most studied mechanism and GIRK channels have not been considered in any detail.

We are interested in whether GIRK channels are present and whether opioid receptors are coupled to GIRK channels on peripheral sensory fibers.

We found no significant expression of any of the 4 mammalian GIRK subunits and no evidence for inwardly rectifying currents in mouse DRG neurons. However, we were able to detect GIRK channels in peripheral sensory neurons of rats and preliminary behavioral experiments demonstrated a difference between the peripheral antinociceptive action of morphine injected into the inflamed paw of mice versus rats. We generated a GIRK2 transgenic mouse in which the GIRK channels are exclusively expressed in a subset of sensory neurons. We hypothesize that the GIRK2 transgenic mice show stronger antinociceptive responses to opioids. If this hypothesis is confirmed, it would indicate that the absence of GIRK2 channels underlies the observed species difference. This would imply that the choice of species is important for the predictive validity of pain models. Furthermore, it will be important to study GIRK channel expression in human DRG neurons and it may be interesting to manipulate GIRK expression by gene therapeutic approaches. Thus, our study will provide new insights into the mechanisms of peripheral opioid analgesia and could lead to new ways to treat pain.

Claudia Nowak

P42 Relationship between oculomotor control and candidate genes for schizophrenia in healthy controls

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The dopamine transporter gene (DAT) has been identified as one of the candidate genes for schizophrenia. However, the mechanistic pathways through which these common polymorphisms increase risk for schizophrenia are unclear.

This study aimed to investigate the functional mechanism of two single nucleotide polymorphisms (SNPs) in DAT1 (rs464049 and rs40184) at the neurocognitive level in a healthy volunteer sample using two well-established oculomotor endophenotypes, the antisaccade (AS) and smooth pursuit eye movement (SPEM) tasks.

A total of 133 healthy Caucasian volunteers completed genotyping for two DAT1 single nucleotide polymorphisms (SNPs); rs464049 and rs40184 and infrared oculographic assessment of SPEM ($n = 99$) and AS (at target velocities of 12°, 24° and 36° per second) were carried out. Differences between genotypes were assessed using repeated measures analysis of variance (ANOVA) including velocity gain/saccadic frequency as dependent variable and genotype and gender as between-subjects factor.

A significant effect of rs464049 and rs40184 genotype was found for SPEM amplitude gain ($P < 0.05$), with an increasing number of G alleles for rs464049 being associated with worse performance on the SPEM task. For rs40184 the results indicate that CT heterozygous carriers perform worse than both homozygous groups on the SPEM task. No statistically significant association was found for other SPEM or AS variables.

DAT1 rs464049 and rs40184 affect spatial accuracy on the SPEM task, suggesting an influence of the gene on the neural mechanisms underlying visospatial sensorimotor transformations, a mechanism that has been previously found to be impaired in patients with schizophrenia and their relatives.

Barbara Pomiechowska, M. Havy, and T. Nazzi

Consonantal bias throughout development – eye-tracking evidence

P43

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Consonants and vowels have been shown to play different functional roles in speech processing and language acquisition: consonants are more important to lexical interpretation while vowels are better cues to syntactic structure. Developmental evidence for this proposal comes mainly from tasks simulating lexical acquisition. While learning new word-object pairings, 16-to-36-month-olds give less weight to vocalic information (Havy, 2009; Nazzi et al., 2009; Nazzi, 2005), displaying a 'consonantal bias'. If, in a task measuring object selection, we present them with unfamiliar objects labeled with new words, differing either by a single consonant (e.g., /pyv/–/tyv/) or a single vowel (e.g., /pyʃ/–/puʃ/), they perform significantly better on the consonantal contrasts. Interestingly, 4- and 5-year-olds do not exhibit this response bias (Havy et al., 2010). However, it remains possible that the consonantal bias might be found using some more sensitive measures not involving overt responses. Thus in order to better discern the evolution of consonantal bias throughout development – whether it persists beyond 3 years of age, and when it emerges – we recorded eye movements of children participating in a visual-choice learning task. We tested 3-, 4- and 5-year-olds and 14-month-olds. They were trained on eight new word-object pairings. Each trial consisted of a familiarization with two word-object pairings and a test during which participants had to look at a requested object. Children's ability to learn words differing either by one consonantal (place of articulation) or one vocalic (height) feature was evaluated with proportion of target looking and response latency to switch from distracter to target. Our results suggest a clear consonantal bias in all 3 preschool age groups, and provide weaker evidence at 14 months, to be further explored.

Eduardo Rosales-Jubal and L. Melloni

P44 Microsaccades rate and magnitude predicts visibility state but do not variate across spatial frequencies

Max Planck Institute for Brain Research, Department Neurophysiology, Frankfurt am Main

Microsaccades are ballistic, involuntary eye movements with small amplitude occurring during fixation. Previous work has documented their contribution to refresh retinal image and counteract visual fading. We investigated the microsaccades dynamics in different spatial frequencies. We compared microsaccades parameters of rate and magnitude in a Troxler effect task using peripheral stimuli of three different spatial frequencies. In line with previous findings, we found a decreased rate and magnitude before periods of visual fading and the opposite effect before the perceptual reappearance of the stimuli. However, and contrary to our prediction, we failed to find a difference between microsaccades' magnitudes preceding periods of visibility across different spatial frequencies, our initial hypothesis being the microsaccades founded in smaller spatial frequencies would present higher magnitudes compared with microsaccades in higher spatial frequencies.

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Investigating the functional network underlying the processing of stereoscopic motion in three-dimensional space: A human fMRI study

P45

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The world surrounding us appears three-dimensional and dynamic. Our visual system has to interpret 3D events from flat 2D retinal images for perception of visual scenes, navigation through the environment and successful interactions with moving objects.

One of the most important visual components is motion away from and towards the observer on the third dimensional axis. How does the human visual system encode three-dimensional motion? Little is known about where in the human brain the binocular motion signals are integrated, but it seems likely that the neural processing of this visual feature is co-localized with other motion relevant areas in the human brain such as the human motion complex (hMT+/V_5). Different classes of dynamic random-dot stereograms (RDS) which contained the relevant features; depth, surface and motion-in-depth, were developed in order to trace the processing phases of the depth and motion components. In a functional Magnetic Resonance Imaging (fMRI) experiment those stimulus conditions were systematically contrasted in a block design. By using retinotopic mapping and a motion localizer it was possible to functionally identify primary visual areas and hMT+ in individual subjects. Motion-in-depth related brain activity was found in an anterior region within the human motion complex. By using a retinotopic mapping technique optimized for dividing the hMT+ in its composed parts, this anterior region could be identified as human MST-d. We conclude that this region plays an important role in combining time varying disparity positions which lead to the perception of motion-in-depth.

Sabrina Trapp and J. Lepsien

P46 Attentional modulation of visual short-term memory load in the intraparietal sulcus

Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig

The functional role of the intraparietal sulcus (IPS) for short-term memory has recently been strengthened by demonstrating a tight correlation between behavioral capacity measures and the fMRI signal (Todd & Marois, 2004; Xu & Chun, 2006). This study investigated whether the load-sensitive, maintenance-related signal in the IPS can be dynamically modulated by selective attention. Selective attention was manipulated by presenting a retro-cue in the retention period, indicating a single item from memory as relevant for further processing (Griffin & Nobre, 2003). Subjects performed a visual STM task with load (2,4,6) and attention (retro-cue, neutral) as factors. It was hypothesized that activity in the IPS would be modulated in the retro-cue condition. A whole-brain-analysis revealed a significant interaction between attention and load at the anterior end of the right IPS. Additional region-of-interest analyses identified other parts of the IPS with load-related reduction of activity for retro-cueing.

Wiebke Warneke,[1] J.-P. Voigt,[2] and H. Fink[1]

Does diet induced obesity affect behaviour? A study to detect impacts of age and gender

P47

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Genetically manipulated animal models are suitable to study mechanisms of human obesity as they are helpful to clarify the involvement of single neurotransmitters and hormones. Since diet induced obesity mimics the evolution of human obesity in a more lifelike way, our intention was to use an animal model of obesity which is based on manipulations of the diet. Given that differences in age and gender often result in contradictory outcomes of similarly conducted tests, we investigated metabolic as well as behavioural changes induced by a so called Cafeteria Diet (CD) in young adult and adult male and female Sprague-Dawley rats. After four weeks of feeding the high caloric CD all animals were tested for their anxiety-related behaviour and learning abilities in the Elevated Plus Maze test, Open Field test and Novel Object Discrimination test (NOD). Additionally, energy intake and body weight gain were documented daily. At the end of the study fat tissue was dissected. Despite their increased energy intake, younger rats were able to resist the development of obesity through compensatory mechanisms whereas adult rats showed an elevated body weight. In all groups fed with CD visceral fat mass was significantly enlarged. Upon behavioural testing, male CD fed rats showed a higher anxiety-related behaviour whereas females seemed to be less anxious than chow fed controls. This discrepancy was more pronounced in the older animals. When exposed to the NOD, all CD fed rats showed better object recognition than controls.

The results show that diet induced obesity goes along with a broad spectrum of behavioural changes. There was a significant impact of age and sex on the development of obesity and the associated behavioural changes.

GRADUATE PROGRAMS

International Graduate Program
Medical Neurosciences

International Master and Doctoral
Program Computational Neuroscience

Berlin School of Mind and Brain

GRK 1123: Cellular Mechanisms of Learning and
Memory Consolidation in the Hippocampal Formation

Helmholtz International Research School
Molecular Neurobiology

International Graduate School Languages of Emotion

NeuroCure

Towards a better outcome of
neurological disorders

MedNeuro

International Graduate Program Medical Neurosciences and Cluster of Excellence "NeuroCure"

Program Coordination Prof. Dr. U. Dirnagl, Prof. Dr. U. Heinemann, Prof. Dr. H. Kettenmann, Prof. Dr. A. Kupsch, Dr. B. Salmen, Prof. Dr. D. Schmitz

Medical Neurosciences focuses on translational research. The main objective is to bridge the gap between successes at the bench and – currently – less than satisfactory treatment at the bedside. The rigorous and comprehensive teaching program provides a structured education in basic neuroscience to medical students and trains students of the life sciences in medical topics and approaches concerning the central and peripheral nervous system.

The MSc program is divided into 5 modules and a research phase including the Master thesis. It is in the research phase that students combine the expertise gained in modules 1 to 5 and investigate a set of questions in great detail, perform experiments, analyze results and write a thesis.

During the 3-year PhD program, students primarily work on their research project in one of the participating labs. In addition to the lab work, they broaden their neuroscience expertise by taking classes and attending colloquia or lecture series. Once a year, PhD students organize an international PhD symposium. The PhD degree is awarded based on three publications or a dissertation.

Cluster of Excellence "NeuroCure" – Scientific Coordinator Prof. Dr. D. Schmitz
NeuroCure is an interdisciplinary consortium uniting neuroscientists, basic researchers, and clinicians on one campus, independent of their institutional affiliations. Building on the strength of the Berlin neuroscience community in the areas of cerebrovascular diseases, neuroinflammation, and disorders of network formation, NeuroCure's initial focus will be on stroke, multiple sclerosis, focal epilepsies, and developmental disturbances. These neurological disorders are known to have overlapping pathophysiological cascades. NeuroCure aims to unravel the underlying mechanisms.

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International Master and Doctoral Program Computational Neuroscience

Spokesperson Prof. Dr. Klaus Obermayer

The Bernstein Center offers an International Master and Doctoral Program in Computational Neuroscience with the goal of training young scientists that will be competent in both computational and experimental neuroscience and will be able to judge scope and limits of theoretical and empirical approaches.

The Master Program, a joint program of Humboldt-Universität and Technische Universität, is articulated in two years. In the first year, students are provided with basic experimental and theoretical techniques. In the second year, they participate in research in laboratories affiliated with the Bernstein Center, facilitating conception and development of their own research project the foundation of their Master Thesis. The Doctoral Program has now merged with the new Graduiertenkolleg "Sensory Computation in Neural Systems" funded by the German Research Council. It gathers doctoral students working on interdisciplinary projects jointly overseen by supervisors of complementary expertise. Experimentalists and theoreticians join forces to educate young scientists to exploit the recent advances in machine learning, theoretical computer science, and statistics for modeling brain function, and to develop new theories of computation hand in hand with well-controlled experiments in order to put functional hypotheses to test.

The doctoral candidates are integrated into Berlin's collaborative teaching and research environment and the National Network for Computational Neuroscience. They participate in the organization of scientific meetings and attend conferences in Germany and abroad an excellent platform to connect to the international neuroscience community.

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Berlin School of Mind and Brain

Spokespersons Prof. Dr. Michael Pauen and Prof. Dr. Arno Villringer

The Berlin School of Mind and Brain is an international doctoral research school. Founded in 2006 and funded by Germany's Excellence Initiative, it offers a three-year interdisciplinary program in English in the mind/brain sciences.

Research within the School focuses on the interface between the humanities and the neurosciences. Of particular interest are research areas that fall on the borders between the mind sciences (e.g., philosophy, linguistics, behavioral and cognitive science, economics), and the brain sciences (e.g., neurophysiology, computational neuroscience, neurology, and neurobiology). Major topics of research within the program include: 'conscious and unconscious perception', 'decision-making', 'language', 'brain plasticity and lifespan ontogeny', 'mental disorders and brain dysfunction', 'philosophy' (philosophy of mind and ethics), and molecular and cellular approaches to cognition (e.g. 'social cognition' and 'autism').

The School has a faculty comprised of 60 distinguished researchers, including five Max Planck directors. Hosted by Humboldt-Universität, the School's research program involves scientists from the Freie Universität, the Charité, the Technische Universität, the Bernstein Center for Computational Neuroscience, and the Max Planck institutes for Human Development and History of Science (all in Berlin), as well as the Max Planck Institute for Human Cognitive and Brain Sciences in Leipzig and the universities of Potsdam and Magdeburg.

Each year the School accepts ten to fifteen doctoral candidates into its program. Throughout the three-year program students attend eight research-related teaching weeks, international lecture series, journal clubs, poster presentations, conferences and workshops. They are obliged to take a number of academic soft-skill courses such as presentation skills, grant-application writing, scientific writing, and are offered dissertation coaching and peer-mentoring.

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Graduate Training Program learning & memory

GRK 1123
Cellular Mechanisms of Learning and Memory Consolidation in the Hippocampal Formation

Spokespersons Prof. Dr. Uwe Heinemann and Prof. Dr. Dietmar Schmitz

The Graduate School offers the possibility to study cellular mechanisms of learning and memory formation as well as memory consolidation. Our understanding of such processes is of outmost interest in biology and medicine as it determines the capability of an organism to adapt to its environment independently of genetically determined behaviors. Consequently, formation of explicit memory is one of the most important aspects of human behavior and is the prerequisite of our individuality. Conversely, disturbance of the cellular and molecular processes underlying learning and memory can result in a variety of neurological and psychiatric disorders. These include devastating diseases such as temporal lobe epilepsy and Alzheimer's disease. The most intensely studied cellular models of learning and memory are LTP (long-term potentiation) and LTD (long-term depression). Many of the underlying pre- and post-synaptic mechanisms are still far from being understood. While short-term memory depends on covalent modifications of preexisting proteins, enduring memory traces need to be consolidated and depend on gene transcription. The specific translated proteins contribute to changes in neuronal circuitry that might comprise the generation of sharp wave ripple complexes, the formation of frequency memories and low frequency-induced heterosynaptic increases in LTP. Moreover, stored information may be replayed in the form of patterns of neuronal activity during REM sleep superimposed on theta and gamma rhythms and thereby cause alterations of synaptic coupling outside the hippocampus proper. Each ofçthe 13 tutors of this graduate school will bring to these problems his or her specific expertise. Using physiological, morphological, cell biological, genetic, and behavioral methods, as well as modeling of neuronal network properties, the students in the graduate school will have the opportunity to contribute to this exciting field of the neurosciences within an excellent environment for training in modern neurobiological methods.

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Helmholtz International Research School "Molecular Neurobiology"

Spokesperson Prof. Dr. Gary Lewin
Deputy Spokespersons Prof. Dr. Volker Haucke and Prof. Dr. Fritz Rathjen

The aim of this research school is to provide state-of-the-art training to elucidate the molecular basis of neurobiological processes. Within this context, students admitted to the research school are expected to pursue a research project designed to understand the molecular basis underlying normal function or dysfunction of the nervous system. Our flexible training curriculum is composed of a two year lecture series covering basic and advanced concepts of Neurobiology, a student journal club, practical courses and PhD-student retreats. In addition, we offer soft skill courses organized by the Helmholtz Association in conjunction with students from other Helmholtz Research Schools encompassing a range of research areas.

Our School's faculty comprises researchers from the Max Delbrück Center for Molecular Medicine, Freie Universität Berlin and Charité – Universitätsmedizin Berlin.

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LANGUAGES OF EMOTION

International Graduate School "Languages of Emotion"

Cluster Coordinator Univ.-Prof. Dr. Winfried Menninghaus

The graduate school offers a structured doctoral training program for 15 young scholars per year. In close exchange with the supervisory team and with cluster researchers, doctoral candidates are able to complete their dissertations in a three-year period. Projects are pursued within individual subject areas, and candidates profit from the expertise of various disciplines, hence becoming integrated from the very start into cutting edge emotion research.

The school offers a three-year PhD program for graduate students who have already earned an MA degree or an equivalent. A "fast track" admission will allow outstanding students who have only completed the first year of their postgraduate MA studies to be accepted as well. "Languages of Emotion" provides ten stipends per year for PhD students in the various disciplines participating in the cluster (among others Anthropology, Film Studies, Japanese Studies, Art History, Musicology, Philosophy, Political Science, Psychology, Psychiatry, Neuroscience, Sociology, Linguistics, Dance and Theater Studies). Up to five additional PhD students per year who have secured funding from sources other than the cluster will be admitted to the program.

All seminars will be co-taught by professors from at least two disciplines. They will be designed to provide the PhD students with a common basis and a shared focus. A seminar of this kind will typically introduce doctoral candidates to interdisciplinary approaches to one of the major research topics of the cluster "Languages of Emotion." In addition, there is a PhD colloquium meant to provide ample opportunity for the students to discuss their work with both tutors and co-students and to learn more about the vast field of emotion research.

Successful students will obtain both a PhD degree from their respective discipline and a second certificate documenting their education at the Cluster of Excellence and their interdisciplinary work on "Languages of Emotion".

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APPENDIX

M

N

P

R

S

T

V

W

Z

For your notes on the opening lecture

For your notes on Session 2

For your notes on Session 4

From **Bahnhof Friedrichstraße**, take S-Bahn line S2 direction Buch/Bernau to S-Bahnhof Berlin-Buch. From there take Bus 351 (direction Campus Buch; bus stop to the left of the train station) directly to MDC (last stop). (Travel time: about 40 min. from Friedrichstraße.)

There is also a taxi stand upon exiting the S-Bahn station Berlin-Buch. The MDC is about twenty minutes' walking distance from the station Berlin-Buch.

S+U Friedrichstr. Bhf (Berlin) ▸ Campus Buch (Berlin)

gültig vom 01.11.2010 bis 03.11.2010

Ab	Fahrt	An	Umsteigen	Ab	Fahrt	An	Dauer
08:00	S2 bh	08:24	S Buch (Berlin)	08:30	Bus 351 bf	**08:38**	00:38
08:10	S2 bh	08:34	S Buch (Berlin)	08:40	Bus 351 bf	**08:48**	00:38
08:20	S2 bh	08:44	S Buch (Berlin)	08:50	Bus 351 bf	**08:58**	00:38
08:30	S2 bh	08:54	S Buch (Berlin)	09:00	Bus 351 bf	**09:08**	00:38
08:40	S2 bh	09:04	S Buch (Berlin)	09:10	Bus 351 bf	**09:18**	00:38
08:50	S2 bh	09:14	S Buch (Berlin)	09:20	Bus 351 bf	**09:28**	00:38
09:00	S2 bh	09:24	S Buch (Berlin)	09:30	Bus 351 bf	**09:38**	00:38

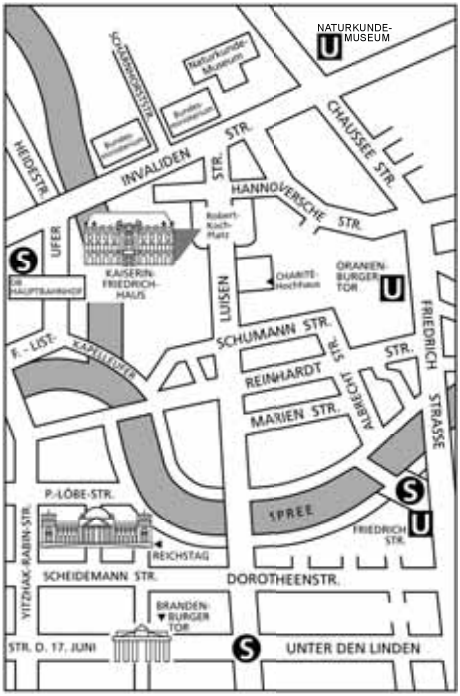
Campus Buch (Berlin) ▸ S+U Friedrichstr. Bhf (Berlin)

gültig vom 01.11.2010 bis 03.11.2010

Ab	Fahrt	An	Umsteigen	Ab	Fahrt	An	Dauer
17:18	Bus 351 bf	17:28	S Buch (Berlin)	17:35	S2 bh	**17:58**	00:40
17:38	Bus 351 bf	17:48	S Buch (Berlin)	17:55	S2 bh	**18:18**	00:40
17:59	Bus 351 bf	18:08	S Buch (Berlin)	18:15	S2 bh	**18:38**	00:39

Legende

bh = barrierefrei
bf = barrierefrei



Kaiserin-Friedrich-Stiftung | Robert-Koch-Platz 7 | 10115 Berlin

Max Delbrück Center for Molecular Medicine, Berlin-Buch
Conference Center MDC.C (labeled 83 on the map), lecture hall “Axon”
Robert-Rössle-Straße 10, 13125 Berlin

The **Berlin Brain Days** 2010 are jointly organized by six Berlin-based neuroscience Ph.D. programs

MDC MAX-DELBRÜCK-CENTRUM FÜR MOLEKULARE MEDIZIN BERLIN-BUCH

Graduate Training Program
"Cellular Mechanisms of Learning and Memory Consolidation in the Hippocampal Formation"
DFG-Graduiertenkolleg 1123

Ph.D. Program
Computational Neuroscience
Bernstein Center for Computational Neuroscience Berlin

Berlin, Charité
International Graduate Program Medical Neurosciences

LANGUAGES OF EMOTION

BERLIN SCHOOL OF MIND AND BRAIN

HUMBOLDT-UNIVERSITÄT ZU BERLIN

www.neuroscience-berlin.de/bbd/