6th International Ph.D. Symposium

Berlin Brain Days

2009/*dec.* 9–11

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Max Delbrück Center for Molecular Medicine Berlin-Buch

Welcome to the Berlin Brain Days 2009

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 doctoral 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. Two research training groups (Graduiertenkollegs) of *Deutsche Forschungsgemeinschaft*, on "Learning and Memory" (GRK 1123 – Cellular Mechanisms of Learning and Memory Consolidation in the Hippocampal Formation) and on "Neuroinflammation" (GRK 1258 – The Impact of Inflammation on Nervous System Function), were established in 2005 and 2006. In this time the Bernstein Center for Computational Neuroscience was launching its own comprehensive doctoral program in computational neuroscience. Also in 2006, as part of the *Excellence Initiative* for German universities, the Berlin School of Mind and Brain was established to foster transdisciplinary research at a doctoral level across the mind and brain sciences. And there have been a second and third acquisition of the *Excellence Initiative*: the excellence clusters "NeuroCure" and "Languages of Emotion", both with funding for doctoral programs.

In December 2008, we very successfully joined our forces for the first time. The Berlin Brain Days 2009 are again a common activity of all these programs. Students and faculty alike are highly motivated to learn about the activities of

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

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

The success of the Berlin Brain Days inspired a previous keynote speaker from Japan to solicit a similar activity in Fukuoka. Last year, Professor Mami Noda joined the Berlin Brain Days with a group of her students from Japan, and this year she organized the first Kyushu Brain Days – and even obtained funds for Berlin students to join in the event. In 2009, we can welcome another interesting group of visitors: the Berlin School of Mind and Brain awarded a women's travel grant to 20 neuroscience, linguistics and philosophy students from Canada, USA, Israel, France, Britain, Spain, Turkey, and Germany. We welcome them to Berlin and look forward to seeing their research as they too will attend the Berlin Brain Days and present posters.

It is in our best interest that we join forces, interact closely, and 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

Wednesday, 9 December 2009
Charité – Universitätsmedizin Berlin | Langenbeck-Virchow-Haus | Luisenstraße 58/59 | 10117 Berlin

Opening lecture

18.30 **Helmut Kettenmann** › opening address
Jörg Geiger "Energetics and signal transmission in cortical non-myelinated axons"

followed by a reception

Thursday, 10 December 2009
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 **Gary Lewin** › Introduction
Elly Tanaka "Cellular and molecular control of axolotl spinal cord regeneration"

10.00 **Valentina Mosienko, Damir Omerbasic** › Ph.D. talks

Session 2

11.00 **John-Dylan Haynes** › Introduction
Andreas Bartels "Color, motion, and natural vision in the human brain"

12.00 **Felix Bießmann, Thorsten Kahnt, Kerstin Hackmack** › Ph.D. talks

13.00 Lunch

13.45 Ph.D. poster presentations (+ coffee) **odd numbers**

Session 3

15.00 **Uwe Heinemann** › Introduction
Gábor Tamás "Value encoding in the human brain"

16.00 **Christian Barucker, Benjamin Rost** › Ph.D. talks

Friday, 11 December 2009

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 **Frank Heppner and Josef Priller** › Introduction
Thomas Möller "Microglia in Huntington's disease – good, bad or something else altogether?"

10.00 **Gina Dji-In Eom, Dinah Nockemann** › Ph.D. talks

Session 5

11.00 **Ulrich Dirnagl** › Introduction
Wolfgang Kuschinsky "Regulation of cerebral blood flow: a story of increasing complexity"

12.00 **Ana I. Oliveira-Ferreira, Martina Füchtemeier** › Ph.D. talks

13.00 Lunch

13.45 Ph.D. poster presentations (+ coffee) **even numbers**

Session 6

15.00 **John-Dylan Haynes** › Introduction
Nancy Kanwisher "Feedback of visual object information to foveal retinotopic cortex"

16.00 **Holger Gerhardt, Radoslaw M. Cichy, Carsten Bogler** › Ph.D. talks

17.00 Award of "Best Poster"

BBD Party

22.00 Das Edelweiss, Görlitzer Str. 1–3 (located in Görlitzer Park), 10997 Berlin-Kreuzberg
Enter Görlitzer Park at Görlitzer Straße 69 or at the corner of Skalitzer Straße and Görlitzer Straße.

Award of "Best Talk"

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OPENING LECTURE

Wednesday, 9 December 2009

18.30 **Jörg Geiger**
Energetics and signal transmission in cortical non-myelinated axons

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

Chair **Dietmar Schmitz**
Charité – Universitätsmedizin Berlin

Jörg Geiger

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2002–2009	Independent Junior Research Group leader at the Max Planck Institute for Brain Research, Frankfurt/Main
1997–2002	Associate Research to Professor Wolfram Schultz, Institut de Physiologie, Université de Fribourg, Switzerland
1995–1996	Ph.D. student at the Institute of Physiology, University of Freiburg under supervision of Professor Peter Jonas
1993–1995	Ph.D. student in the department of cell physiology, Max Planck Institute for Medical Research, Heidelberg, under the supervision of Professor Peter Jonas
	Member of the graduate program "Molecular and cellular neurobiology," University of Heidelberg
1986–1992	Study of biology and physics at Freie Universität Berlin; external diploma thesis in the Biophysics Group, Department of Physics (Professor Peter Fromherz), Ulm University

Jörg Geiger

Energetics and signal transmission in cortical non-myelinated axons

Institute of Neurophysiology, Charité – Universitätsmedizin Berlin

Understanding the distribution of the energy budget for neural information processing is of key importance for determining the metabolic constraints on brain function. It also has crucial practical and clinical implications for the interpretation of metabolism-dependent recordings of brain activity such as the BOLD signal in fMRI. Action potentials are the core electrical signals of the brain, and have been suggested to consume a large portion of the energy expended on neural activity in the mammalian gray matter implying a tight correlation of energy demand and action potential rates. This view has generated considerable controversy, particularly given the lack of correlation between metabolism-dependent recordings of brain activity and action potential rates in vivo, which directly challenges this view. Unfortunately, there has been no direct experimental data regarding action potential energetics at the cellular level, particularly in non-myelinated gray matter axons, where the largest energy demand of action potentials is expected. Previous calculations have relied on extrapolations from the classical studies of Hodgkin & Huxley on squid giant axons, which generate action potentials of extremely low energy efficiency due to overlap of underlying ionic currents. Direct recordings at physiological temperatures from non-myelinated mossy fiber axons in rat hippocampal slices led to the discovery that regenerative action potentials in non-myelinated axons of mammalian cortex are remarkably energy-efficient, implying a surprisingly minor contribution of action potentials to the entire energy expenditure of neural information processing. The same approach also allowed to determine the passive properties of mammalian non-myelinated axons and the accompanying energy consumption to maintain axonal resting membrane potential. Cortical non-myelinated axons are tight structures, keeping the energy demand to counteract leak currents low. This leads directly to conduction of subthreshold, analog signals generated in the dendrites of neurons down the non-myelinated axons to proximal presynaptic elements. The analog presynaptic signals encode additional output information which are decoded and co-transmitted at the synapse in combination with action potentials. Both, energy-efficiency of action potentials and combined analog and digital signal transmission emphasize that cortical non-myelinated axons are optimized to transmit maxinmal information at minimal costs.

SESSION 1

Thursday, 10 December 2009

9.00 **Elly Tanaka**
Cellular and molecular control of axolotl spinal cord regeneration

10.00 **Valentina Mosienko**
Damir Omerbasic
› Ph.D. talks

Introduction **Gary Lewin**
Max Delbrück Center for Molecular Medicine
Berlin-Buch

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

Elly Tanaka

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2007–present	Professor for Animal Models of Regeneration, DFG Center for Regenerative Therapies Dresden
1999–2007	Group Leader at the Max Planck Institute of Molecular Cell Biology and Genetics, Dresden
1994–1999	Post-doctoral fellow, Ludwig Institute for Cancer Research, London and University College London, UK, Department of Biochemistry and Molecular Biology
1987–1993	Ph.D., Department of Biochemistry, University of California, San Francisco, USA

Elly Tanaka, A. Tazaki, and L. Mchedlishvili

Cellular and molecular control of axolotl spinal cord regeneration

Center for Regenerative Therapies Dresden, Technische Universität Dresden

Salamanders have the amazing capability of regenerating central nervous system structures such as the retina, the brain and the spinal cord after injury. We have studied the cellular and molecular events that occur after spinal cord injury leading to regeneration. Our results indicate that injury activates stem cell renewal in the first 500 µm of spinal cord away from the injury site. There, the cells revert to an immature state, where they show neuroepithelial properties. Once activated, the cells undergo symmetric divisions for about one week before neurogenesis begins in a rostral-caudal wave. Sonic hedgehog seems to be a primary determinant of neural stem cell division in this system. Beyond identifying the signals that convert spinal cord cells to an immature state, we are pursuing whether such signals can stimulate mammalian cells to undergo a similar transition.

Valentina Mosienko, N. Alenina, D. Kikic, M. Todiras, S. Matthes, B. Bert, H. Fink, and M. Bader

Growth retardation, impaired autonomic control, and altered behavior in mice lacking brain serotonin

Molecular Biology of Peptide Hormones,
Max Delbrück Center for Molecular Medicine Berlin-Buch

Tryptophan hydroxylase 2 (TPH2) is a rate limiting enzyme of the serotonin synthesis in the brain. Tph2-deficient mice, which lack central serotonin, were recently generated in M. Bader's lab. Surprisingly, these mice can be born, but exhibit growth retardation in the first 4 weeks of postnatal life. However after weaning, they catch up to the size of controls and survive until adulthood. Telemetric monitoring revealed impairment in the regulation of autonomic functions in normal and stressed conditions in Tph2–/– mice, demonstrating that central serotonin is not essential for life but is a pivotal modulator of numerous autonomic pathways.

Using Tph2-deficient mice we assessed the role of the central serotonin in the regulation of anxiety and maternal behavior. Tph2–/– mice displayed behavior associated with reduced anxiety as indicated in an elevated plus maze and buried marble tests. Moreover, Tph2–/– mothers despite being fertile and producing milk exhibited impaired maternal care leading to less then 45% survival of their offspring. However, in cross-fostering experiments pups from Tph2–/– dams, nursed by wild type mother had normal survival rate, indicating that maternal neglect of Tph2–/– mice is not caused by abnormal development of their pups. Further analysis revealed that Tph2–/– dams were not able collect their scattered pups in the pups-retrieval test confirming alteration in maternal instinct. However, Tph2–/– female did no show any difference in the hidden cookie and olfactory recognition tasks indicating that maternal neglect is not associated with disturbed olfaction in Tph2–/– mice. Our findings suggest an important role for serotonin signaling in maternal instinct and anxiety-associated behavior.

Damir Omerbasic, E. S. J. Smith, and G. Lewin

Molecular dissection of sensory phenotypes using the naked mole-rat (Heterocephalus glaber)

Molecular Physiology of Somatic Sensation,
Max Delbrück Center for Molecular Medicine Berlin-Buch

The naked mole-rat (NMR) (Heterocephalus glaber) is an unusual subterranean rodent native to East Africa. Subsequent to its discovery, research has revealed many interesting ecological and physiological features. Some of these include eusociality, longevity and poikilothermy. The study of the unique features seen in extremophile mammals such as the NMR has the potential to provide a better and deeper insight into 'normal' physiology. It is known that a distinct population of C-fibre nociceptors expresses TrkA, the high-affinity receptor for nerve growth factor (NGF), and that binding of NGF to TrkA leads to subsequent phosphorylation of the ion channel TRPV1 which results in its sensitization and development of thermal hyperalgesia. Interestingly, thermal hyperalgesia is absent in NMRs, whether provoked by inflammation or by known sensitization agents like capsaicin or NGF. These findings in the NMR point towards hypo-functional NGF-TrkA signalling in this species. The goal of this project is to elucidate what factors in NGF-TrkA signalling are specifically altered in the NMR with particular interest focused on proteins involved in signalling pathways in heat hyperalgesia (TrkA, PLCγ PI_3 kinase, Ras-Map kinase etc.).

SESSION 2

Thursday, 10 December 2009

11.00 **Andreas Bartels**
Color, motion, and natural vision of the human brain

12.00 **Felix Bießmann**
Thorsten Kahnt
Kerstin Hackmack
› Ph.D. talks

Introduction **John-Dylan Haynes**
Bernstein Center for Computational Neuroscience Berlin

Chair **Vinzenz H. Schönfelder**
International Doctoral Program Computational Neuroscience

Andreas Bartels

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present	Group leader at the Werner Reichardt Centre for Integrative Neuroscience & MPI, Tübingen, Germany
2004–2009	Max Planck Institute for Biological Cybernetics, Tübingen, Germany Fellowship from Swiss National Science Foundation (till 2006) and Max Planck fellowship
2003	UCL Bogue Fellow UCSD, ERP Lab, University of California, San Diego, USA
2001–2003	Post-Doctoral Research Scientist University College London, UK
1997–2001	Ph.D. (Marie Curie Fellow) University College London, UK
1996–1997	Diploma thesis The Salk Institute, Computational Neurobiology, San Diego, California, USA
1992–1997	University of Zurich, Switzerland Diploma in Zoology/Neurobiology/Molecular Genetics

Andreas Bartels

Color, motion, and natural vision in the human brain

Centre for Integrative Neuroscience and Max Planck Institute for Biological Cybernetics, Tübingen, Germany.

Humans are primarily visual beings, and my talk is about visual perception and processing in the human brain. I will first review some of the classic evidence of functional specialization – the counterintuitive organization principle that features such as color and motion are processed in separate pathways. Next I will present consequences of this – psychophysical evidence (a demonstration plus data) for the slowness of visual feature binding, and the latest fMRI evidence for specialized loci within V1 representing bound features.

In the second half of the talk will deviate from well-controlled studies, and describe imaging approaches to study brain function in natural conditions, when subjects view movies. I will demonstrate that not only specialized regions, such as FFA, V4 and V5/MT can be mapped, but also retinotopy and tonotopy, using entirely uncontrolled data.

Finally, I will use the same movie data to present evidence for segregated processing of ego-motion and object-motion in the parietal cortex.

Felix Bießmann, F. C. Meinecke, Y. Murayama, N. K. Logothetis, K. R. Müller

Neurovascular coupling dynamics in primary visual cortex during spontaneous activity

Machine Learning Group, Theoretical Computer Science,
Technische Universität Berlin

Neural activity in the brain is correlated with the blood-oxygen level dependent (BOLD) contrast which can be measured non-invasively by functional magnetic resonance imaging (fMRI). Up to date, many fMRI analysis methods are based on simplifying assumptions about the nature of the BOLD signal. There are two common assumptions that might lead astray interpretations of experimental results: For one, fMRI data has spatial dependencies; each fMRI voxel might be strongly correlated with some voxels but not with others. These spatial dependencies are neglected in many analysis methods by assuming statistical independence between voxels. Secondly, the BOLD response to neural activity is not instantaneous and the exact shape of the hemodynamic response function (HRF) changes, e.g., across subjects. Most fMRI analyses do not take this variability into account and assume a canonical HRF.

In this study we employ a recently developed machine learning algorithm to estimate the spatial correlation structure and the temporal dynamics of the hemodynamic response to spontaneous neural activity. We present results from simultaneous recordings of neural activity and BOLD response in primary visual cortex (V1) of the non-human primate. Our results confirm well established models of the HRF and reveal the spatial correlation structure in V1. The spatial pattern that correlates best with neural activity can be used to study functional connectivity. This connectivity measure does not depend on model assumptions about neural activity or neurovascular coupling mechanisms. In contrast the connectivity pattern is computed directly from intracranially measured neural activity and thereby complements existing functional connectivity measures that are based on fMRI data only.

Thorsten Kahnt,[a, b, c] J. Heinzle,[a] S. Q Park,[c, d] and J.-D. Haynes[a, b, c]

The neural code of reward anticipation in human orbitofrontal cortex

[a] Bernstein Center for Computational Neuroscience Berlin
[b] Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig
[c] Berlin School of Mind and Brain, Humboldt-Universität zu Berlin
[d] Max Planck Institute for Human Development, Berlin

An optimal choice among alternative behavioral options requires precise anticipatory representations of their possible outcomes. A fundamental question is how such anticipated outcomes are represented in the brain. Reward signals arising from dopaminergic midbrain neurons have been suggested to broadcast value information to the prefrontal cortex. However, the exact format of reward representations in cortical areas has remained unclear. Reward coding at the level of single-cells follows a more heterogeneous coding scheme than suggested by studies using functional magnetic resonance imaging (fMRI) in humans. Using a combination of multivariate pattern classification and fMRI we show that the reward value of sensory cues is encoded in distributed response patterns in the orbitofrontal cortex. This distributed encoding is compatible with previous reports from animal electrophysiology showing that reward is encoded by different neural populations with opposing coding schemes. Importantly, the response patterns encoding specific values during anticipation are similar to those that emerge during the receipt of reward. Furthermore, we show that the degree of this similarity is related to subjects' ability to use value information to guide behavior. These results bridge the gap between reward coding in human and animals and corroborate the notion that value representations in prefrontal cortex are independent of whether reward is anticipated or actually received.

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

Decoding multiple sclerosis from MRI brain patterns

Theory and Analysis of Large-Scale Brain Signals,
Bernstein Center for Computational Neuroscience Berlin

Recently, pattern recognition approaches have been successfully applied in the field of clinical neuroimaging in order to differentiate two clinical groups. Here, those multivariate decoding algorithms are used to detect patients suffering from multiple sclerosis (MS) in contrast to healthy controls on the basis of structural MR images.

Structural MR images of 41 MS patients and 26 healthy volunteers entered the analysis. After normalizing the images, we used a two-stage procedure in order to classify the resulting images into MS and non-MS. In the first step, independent classifiers are trained on local brain patterns using a searchlight approach. By employing a (nested) cross-validation scheme, we obtained accuracy maps for each region in the brain. In the second step, we used an ensemble approach to combine the information of best discriminating brain regions in order to make a final decision towards MS or non-MS for a novel image. To predict symptom severity, a further regression analysis within MS patients regarding different clinical markers was applied.

By using ensembles the clinical condition could be predicted with 90% accuracy. A nearly perfect separation could be observed for thalamic regions, basal ganglia and hippocampus. Additionally, it turned out that clinical measures mainly assessing the lower and upper extremity function could not be predicted on the basis of the structural images. However, the PASAT score, a measure of cognitive function, could be well decoded from the superior temporal lobe.

To our best knowledge this is the first pattern recognition approach to diagnose MS. With an accuracy of 90%, clinical applications are conceivable. The identification of thalamic regions based on pattern recognition methods is novel and matches with a recent report on a higher degree of thalamic atrophy in MS as compared to controls.

SESSION 3

Thursday, 10 December 2009

15.00 **Gábor Tamás**
Single cell driven GABAergic volume transmission in cortical circuits

16.00 **Christian Barucker**
Benjamin Rost
› Ph.D. talks

Introduction **Uwe Heinemann**
Institute of Neurophysiology,
Charité – Universitätsmedizin Berlin

Chair **Gürsel Çalışkan**
GRK 1123 Cellular Mechanisms of Learning and Memory

Gábor Tamás

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1997–2002	Professor University of Szeged, Department of Comparative Physiology, Szeged, Hungary
1996–1997	European Blaschko Visiting Research Scholar University of Oxford, MRC Anatomical Neuropharmacology Unit, Oxford, United Kingdom
1997	Ph.D. in Neuroscience József Attila University in Szeged

Gábor Tamás

Single cell driven GABAergic volume transmission in cortical circuits

Department of Physiology, Anatomy and Neuroscience, University of Szeged, Hungary; Hungarian Academy of Sciences Research Group for Cortical Microcircuits

Gamma-aminobutyric acid (GABA) is predominantly released by local interneurons in the cerebral cortex to particular subcellular domains of the target cells. This suggests that compartmentalized, synapse specific action of GABA is required in cortical networks for phasic inhibition. However, GABA released at the synaptic cleft diffuses to receptors outside the postsynaptic density and thus tonically activates extrasynaptic GABAA and GABAB receptors, which include subtypes of both receptor families especially sensitive to low concentrations of GABA. The synaptic and extrasynaptic action of GABA is in line with idea that neurons of the brain use synaptic (or wiring) transmission and nonsynaptic (or volume) transmission for communication. However, reuptake mechanisms restrict the spatial extent of extrasynaptic GABAergic effects and it was proposed that concerted action of several presynaptic interneurons or sustained firing of individual cells or increased release site density is required to reach ambient GABA levels sufficient to activate extrasynaptic receptors. We find that individual neurogliaform cells release GABA sufficient for volume transmission within the axonal cloud and thus neurogliaform cells do not require synapses to produce inhibitory responses in the overwhelming majority of nearby neurons.

Neurogliaform cells suppress connections between other neurons acting on presynaptic terminals which do not receive synapses at all in the cerebral cortex. Moreover, neurogliaform cells reach extrasynaptic, δ subunit containing GABAA receptors responsible for tonic inhibition and reveal that δ subunit containing GABAA receptors are localized to neurogliaform cells preferentially among cortical interneurons. Neurosteroids and ethanol, which are modulators of δ subunit containing GABAA receptors alter unitary GABAergic effects between neurogliaform cells. In contrast to the specifically placed synapses formed by other interneurons, the output of neurosteroid and ethanol sensitive neurogliaform cells represents the ultimate form of spatial unspecificity in GABAergic systems leading to long lasting network hyperpolarization combined with widespread suppression of communication in the local circuit.

Christian Barucker and G. Multhaup

The β-amyloid peptide (Aβ) in processes of learning and memory: a possible role in the nucleus

GRK 1123 Cellular Mechanisms of Learning and Memory

The amyloid precursor protein (APP) is central to the pathogenesis of Alzheimer's disease (AD). APP is a type I transmembrane protein which is cleaved by the β-site-APP-cleaving enzyme (BACE) and the gamma-secretase complex to generate Aβ peptides and the APP intracellular domain (AICD). The pathogenic effects observed in AD are ascribed to soluble low-n oligomers of Aβ42. Recently, we could show that toxicity of Aβ is not a simple cause of Aβ oligomerization but a consequence of the adoption of a specific conformation determined by the GxxxG interaction motif. This motif is contained within the hydrophobic C-terminus of the Aβ peptide and places two glycines on the same face of a β sheet. We have discovered a possible role for Aβ in gene regulation, which could either represent a normal or a gain-of-function of Aβ. Aβ peptides of varying lengths are actively transported to the nucleus where they accumulate in a time-dependent manner. Aβ42 decreased or increased mRNA levels of specific genes. We postulate that the toxic mechanism of Aβ could be mediated through the interaction of Aβ with genomic DNA and, thereby, Aβ could ultimately affect gene expression. Since intraneuronal Aβ has been recognized as relevant for the pathogenesis, Aβ internalization and its gene regulating activity could be important in AD.

Benjamin Rost and D. Schmitz

Mechanisms of presynaptic inhibition by GABAb receptors

Neuroscience Research Group; NeuroCure, Charité – Universitätsmedizin Berlin

Synaptic transmitter release is tightly controlled by the protein machinery of the presynaptic terminal. G-protein coupled receptors that integrate heterosynaptic or autosynaptic signals can decrease the release probability by inhibiting calcium influx through voltage gated calcium channels, but can also modulate vesicular exocytosis by other means. It has been proposed that GABAb receptors inhibit transmitter release downstream of calcium channels, but the exact mechanism is unclear. We now address the question whether G-proteins activated by GABAb receptors directly interfere with the release machinery of glutamatergic neurons in the mammalian central nervous system. By combining field recordings and photodiode measurements of calcium transients visualized with Magnesium Green AM we established a power function for the calcium dependency of transmitter release at Schaffer collateral synapses. We found that GABAb receptor activated by Baclofen reduce fEPSP amplitude to a greater extend than expected from the reduction of presynaptic calcium influx alone. In CA1, Baclofen reduced the frequency of mEPSCs in calcium free conditions, further indicating that inhibition of transmitter release may also act independently of calcium channels. For a detailed analysis of the underlying mechanisms we used autpatic cultures of primary hippocampal neurons. By fast application of hyperotonic sucrose solutions we directly tested whether Baclofen increases the energy barrier of transmitter release. The size of the readily releaseable pool was not decreased by GABAbR, but the number of vesicles released by submaximal sucrose stimuli was markedly reduced. Our data indicate that presynaptic GABAb receptor activation decreases the fusion willingness of synaptic vesicles by directly interfering with the release machinery.

SESSION 4

Friday, 11 December 2009

9.00 **Thomas Möller**
Microglia and Huntigton's disease – good, bad or something else altogether?

10.00 **Gina Dji-In Eom**
Dinah Nockemann
› Ph.D. talks

Introduction **Frank Heppner and Josef Priller**
Charité – Universitätsmedizin Berlin

Chair **Stefanie Seifert**
GRK 1132 Cellular Mechanisms of Learning and Memory Consolidation in the Hippocampal Formation

Thomas Möller

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present	Research Associate Professor University of Washington, School of Medicine, Neurology
2000–2005	Research Assistant Professor University of Washington, School of Medicine, Neurology
1998–2000	Acting Assistant Professor University of Washington, School of Medicine, Neurology
1998–1998	Senior Research Fellow University of Washington, School of Medicine, Neurology
1997–1998	Visiting Scholar University of Washington, School of Medicine, Neurology
1996–1997	Postdoctoral Fellow Max Delbrück Center for Molecular Medicine Berlin-Buch
1993–1996	Ph.D., Freie Universität Berlin, Neuroscience

Thomas Möller

Microglia in Huntington's disease – good, bad or something else altogether?

University of Washington, Department of Neurology, Seattle, USA

Neuroinflammation is a prominent feature of many neurodegenerative diseases, however, little is known about the role of neuroinflammation in Huntington's disease (HD). We assessed the levels of neuroinflammation-associated mediators in the striatum, cortex and cerebellum from post-mortem HD patient samples to controls. We found increased expression of several key inflammatory mediators, including CCL2 and IL-10, specifically in the striatum of HD patients, the main area affected by this pathology. Remarkably, we also found upregulation of IL-6, IL-8 and MMP-9, in the cortex and notably the cerebellum, a brain area commonly thought to be spared by HD.

Microglial cells, the macrophage population of the CNS, are the main mediators of neuroinflammation. Having found a profound neuroinflammatory response in human HD we investigated whether expression of mutant huntingtin would change common cell biological parameters of microglial cells. Using primary microglial from murine HD models or virally transduced mouse cell lines, we indeed found that huntingtin modulates selective aspects of microglial physiology.

Our data suggest that neuroinflammation is a prominent feature associated with HD and may constitute a novel target for therapeutic intervention.

Gina Dji-In Eom, I. Papageorgiou, R. E. Kälin, O. Kann, and F. L. Heppner

Functional assessment of microglia in central nervous system homeostasis using a mouse model allowing selective ablation of microglia

Neuropathology, Charité – Universitätsmedizin Berlin

Recent findings point towards a greater need to understand the highly versatile state of microglia in the absence of disease, i.e., the "resting" state of microglia, and its contribution to central nervous system homeostasis. In order to address this question, we use a CD11b-promoter driven herpes simplex virus thymidine kinase (HSVTK) transgenic mouse model for selective ablation of microglial cells upon the treatment of ganciclovir. Our procedure results in a high (> 92%) microglial ablation efficiency upon local administration of ganciclovir, while it does not disturb peripheral (systemic) CD11b cells. We conclude that this protocol is an efficient and ideal prerequisite to assess parameters indicative of potential microglia-associated alterations in neuronal circuitry.

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

Characterization of GIRK channels in peripheral sensory neurons of mice and rats

Clinic for Anaesthesiology and Operative Intensive Care,
Charité – Universitätsmedizin Berlin

The G-protein coupled inward rectifying K^+ (GIRK) channels contribute to the postsynaptic inhibition triggered by many neurotransmitters. They are downstream effectors of G-protein coupled receptors and can be activated by direct binding of the β/γ subunit. Opioids belong to the neurotransmitters, which can activate GIRK channels. They act through G-protein-coupled receptors (μ, δ, κ) located on central and peripheral sensory neurons. Apart from activating GIRK channels, opioids also inhibit voltage-gated Ca^{2+} channels. Interestingly, in peripheral sensory 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 opioids are coupled to GIRKs on peripheral sensory fibers. Furthermore, we investigated the role of GIRK/opioid receptor coupling in a model of inflammatory pain.

We found no significant expression of all four GIRK subunits in sensory neurons of mice using RT-PCR and immunohistochemistry. No change in the expression level could be observed after inflammation of the mouse hindpaw. We found mRNA and protein expression of the subunits GIRK1 and 2 in peripheral sensory neurons of rats, but again there was no change in the expression level after inflammation of the hindpaw. We also investigated functional coupling of GIRK channels and opioid receptors in peripheral sensory neurons using patch clamping. We found no evidence for GIRK currents in mouse and rat DRG neurons. Our data indicate that GIRK channels are not significantly expressed in sensory neurons of mice and do not contribute to inhibition of electrical excitability.

GIRK channels are expressed in rat DRG but they are not coupled to μ-opioid receptors. Whether GIRK channels are coupled to δ- or κ-opioid receptors and whether they contribute to peripheral analgesia in rats needs to be investigated.

SESSION 5

Friday, 11 December 2009

11.00 **Wolfgang Kuschinsky**
Regulation of cerebral blood flow:
a story of increasing complexity

12.00 **Anna I. Oliveira-Ferreira**
Martina Füchtemeier
› Ph.D. talks

Introduction **Ulrich Dirnagl**
Experimental Neurology, Charité – Universitäts-
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Chair **Anna Maslarova**
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1979–1980	Research Assistent, National Institutes of Health, Bethesda, M.D., USA
1969	Dissertation, Medical School, University of Munich
1968–1982	Research Assistant, Institute for Physiology, University of Munich

Wolfgang Kuschinsky

Regulation of cerebral blood flow: a story of increasing complexity

Department of Physiology and Pathophysiology, University of Heidelberg

Coupling describes the fact that the regional blood flow in the brain is immediately adjusted to the changing activity of the brain tissue at any moment. This is achieved by two features of cerebral blood flow: 1. the basal rate of cerebral blood flow per brain weight is high compared to other organs, and 2. the variations of cerebral blood flow during changes in functional activity are smaller than in other organs. These two properties of brain tissue make it possible that an efficient coupling can be achieved between brain activity and blood flow by the transmission of comparably moderate signals from the brain tissue to the brain vessels. However, the system of regulation is highly efficient under normal conditions.

An important consequence of the high basal blood flow in the brain is the existence of a stable pool of the main fuel of the brain, i.e. glucose. The glucose concentration in the brain tissue is only about one third of the plasma concentration. Therefore, the glucose pool of the brain tissue is small. It is stabilized by the high blood flow and the large kinetic constants k_1 for the influx of glucose from plasma to the brain precursor pool and k_2 for the backflux of glucose from the precursor pool to plasma. Compared to these, the kinetic constant k_3 for the phosphorylation of glucose is small. This combination of kinetic constants results in a stable concentration of available glucose under normal conditions. This stability of the small glucose pool in brain tissue is also reflected in a small arterio-venous difference of glucose of only 10% under normal conditions.

During pathophysiological conditions, the glucose concentration in the precursor pool is not sufficient to supply the brain with enough glucose. One rare situation in which this happens is the existence of defective glucose transporters at the blood- brain barrier. The low glucose concentrations result in mental retardation in childhood and can be effectively treated by a ketotic diet. Much more often, low glucose concentrations can be found in hypoglycaemia and ischemic diseases. An extreme depletion of glucose exists when increased glucose utilization is combined with a decreased blood flow, as it occurs in CSD and PID. This is a potentially detrimental situation.

The mechanisms which mediate the coupling of neuronal activity to cerebral blood flow can be described in a story of increasing complexity. Starting with the pH hypothesis the multifactorial nature of coupling became soon apparent when K^+ ions and their multiple roles in coupling were identified. Endothelium (e.g., NO) and pericytes (as capillary regulators) as well as astrocytes (e.g., arachidonic acid derivatives) have a role in the adjustment of blood flow to the needs of the tissue. Their effects add to those of neurogenic factors (in this context, factors released by interneurons become of interest in addition to the classical factors), of physical factors, (like transmural pressure, shear stress of endothelium) and of classical metabolic factors. It will be a long way to identify the role of these factors during pathophysiological conditions.

Ana I. Oliveira-Ferreira, M. Alam, S. Major, D. Milakara, and J. P. Dreier

Does Endothelin-1 induce cortical spreading depolarization (CSD) via a direct effect on the vasculature?

Experimental Neurology, Charité – Universitätsmedizin Berlin

Objectives: Endothelin-1 (ET-1) has attracted increasing interest since its discovery by Yanagisawa in 1988. Recognized as a neuropeptide with neurotransmitter/neuromodulator functions, ET-1 is also a potent vasoconstrictor. Moreover, it potently induces CSD in vivo. ET-1 has been related to several pathophysiogical states including subarachnoid hemorrhage, ischemic stroke and traumatic brain injury. The mechanism by which ET-1 induces CSD is not fully understood. Here we further analyzed whether ET-1-induced CSD is preceded by significant pial vasoconstriction and characterized pH changes and electrocorticogram (ECoG).
Methods: We used a two cranial window model in rats (n = 11). ET-1 was brain topically applied in one window at 100 nM and 1 μM. A second window served as control. DC/AC-ECoG and laser-Doppler flowmetry were used to detect CSD. The pial arterioles were imaged onto a camera to assess whether significant vasoconstriction precedes ET-1-induced CSD. The images were analyzed using MATLAB and the diameter change was calculated over time. In another six experiments we recorded the pH changes associated with ET-1-induced CSD using pH-sensitive microelectrodes.
Results: We observed a cluster of recurrent CSDs starting from the ET-1 superfused window and propagating to the control window. The cluster was associated with a negative DC shift of −2.6 ± 2.2 mV on which transient negative DC shifts of CSDs were riding. This was accompanied by a positive DC shift of 0.9 ± 0.9 mV in the control window superimposed with transient negative DC shifts. The magnitude ET-1 induced vasoconstriction was significantly more pronounced in medium and small compared to large arterioles. Only in the presence of ET-1 a pH reduction preceded the sharp alkaline shift of the CSD in all experiments.
Conclusion: The pattern of the DC potential changes, the arteriolar constriction and pH reduction prior to the first cluster of CSDs support the notion that ET-1 induces CSDs due to its vasoconstrictive action. Our data may have implications for clinical conditions ranging from migraine to subarachnoid hemorrhage and ischemic stroke.

Martina Füchtemeier, C. Leithner, N. Offenhauser, M. Kohl-Bareis, U. Dirnagl, U. Lindauer, and G. Royl

Influence of elevated intracranial pressure on neurovascular coupling

Experimental Neurology, Charité – Universitätsmedizin Berlin

Functional MRI with BOLD localizes activated brain areas by measuring decreases of deoxygenated hemoglobin (deoxy-Hb) caused by neurovascular coupling. Its clinical application is directed at localizing eloquent brain areas for neurosurgical interventions, mainly in patients with brain tumors. Surprisingly, elevated intracranial pressure (ICP), a very common condition in these patients, has not yet been studied in its effects on neurovascular coupling. We here ask the question whether ICP elevation modifies brain mapping based on oxygenation changes, e.g., BOLD fMRI. In addition, by elevating ICP we can test the hypothesis that the BOLD post-stimulus undershoot, a regularly seen transient hypo-oxygenation after the end of a functional activation response, is due to passive vascular compliance rather than due to active vascular regulation or to an elevated cerebral metabolic rate of oxygen ($CMRO_2$).

In anesthetized rats, a catheter was positioned inside the cisterna magna. Over the somatosensory cortex, a closed cranial window was implanted. Using laser Doppler flowmetry and optical spectroscopy, changes in cerebral blood flow (CBF), cerebral blood volume (CBV), deoxy-Hb and $CMRO_2$ were measured, interleaved by blocks of electrical forepaw stimulation. In between stimulation blocks, intracranial pressure was adjusted to four different levels (3.5, 7, 14, 28 mmHg) by infusion of artificial cerebrospinal fluid.

ICP elevation did not abrogate neurovascular coupling. However, the concomitant deoxy-Hb decrease was reduced and reversed. Therefore, the validity of BOLD fMRI has to be questioned when ICP is elevated. Moreover, the amplitude of the deoxy-Hb post-stimulus overshoot was reduced with inceased ICP. $CMRO_2$ was not elevated during the post-stimulus response. These data provide experimental evidence that the BOLD post-stimulus undershoot is a passive vascular phenomenon.

SESSION 6

Friday, 11 December 2009

15.00 **Nancy Kanwisher**
Feedback of visual object information to foveal retinotopic cortex

16.00 **Holger Gerhardt**
Radoslaw M. Cichy
Carsten Bogler
› Ph.D. talks

Introduction **John-Dylan Haynes**
Bernstein Center for Computational Neuroscience Berlin

Chair **Radoslaw M. Cichy, Holger Gerhardt**
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Nancy Kanwisher

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1997–present	Investigator at the McGovern Institute and Professor in the Department of Brain and Cognitive Sciences, MIT
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1990–1994	Assistant and Associate Professor, Department of Psychology, UCLA
1988–1990	Assistant Research Psychologist, Department of Psychology, UC Berkeley
1987–1988	Postdoctoral Fellow, Department of Psychology, Harvard University
1986–1987	Visiting Scholar, Institute for War and Peace Studies, Columbia University
1986	Ph.D., Massachusetts Institute of Technology (Cognitive Psychology)

Nancy Kanwisher

Feedback of visual object information to foveal retinotopic cortex

Massachusetts Institute of Technology, McGovern Institute for Brain Research, Cambridge, USA

The mammalian visual system contains an extensive web of feedback connections projecting from higher cortical areas to lower areas, including primary visual cortex. Although multiple theories have been proposed, the role of these connections in perceptual processing is not understood. We found that the pattern of functional magnetic resonance imaging response in human foveal retinotopic cortex contained information about objects presented in the periphery, far away from the fovea, which has not been predicted by prior theories of feedback. This information was position invariant, correlated with perceptual discrimination accuracy and was found only in foveal, but not peripheral, retinotopic cortex. Our data cannot be explained by differential eye movements, activation from the fixation cross, or spillover activation from peripheral retinotopic cortex or from lateral occipital complex. Instead, our findings indicate that position-invariant object information from higher cortical areas is fed back to foveal retinotopic cortex, enhancing task performance.

Holger Gerhardt, L. Mechtenberg, J. Rieskamp, G. Biele, and H. R. Heekeren

How does prior probability influence visual perception?

Institute of Economic Policy, School of Business and Economics,
Humboldt-Universität zu Berlin; Berlin School of Mind and Brain

The process by which sensory information is combined with prior information and used to influence behavior is referred to as perceptual decision making (DM). On the neural level, this is reflected by the accumulation and integration of sensory evidence about different alternatives in specific brain regions. Theoretical accounts of perceptual DM regard prior information as essential for the DM process. It is still largely unknown, however, how and where the brain integrates prior information with current sensory evidence. Specifically, it is unclear whether—and if so, how—prior probabilities (PPs) affect people's percepts of the stimuli, or whether the percepts remain unaffected and integration of evidence and PPs occurs later in the process.

We addressed this question using fMRI and a face–house discrimination task ($n = 21$). We used an event-related design, in which participants were first told the probability of the next stimulus being a face or a house, followed by a 2-second expectation phase and display of the target stimulus (100 ms). Preliminary analyses indicate that PPs had an effect on behavior in 11 participants: Hit rates (and false-alarm rates) for both faces and houses increased with increasing PP of the respective stimulus type, while response times decreased.

Changes in fMRI signal in the left fusiform gyrus during the response phase correlated significantly with the prior probability of the stimulus being a face, independent of the stimulus type actually being shown. During the expectation phase, fMRI signal changes in motor areas correlated significantly with the prior probability at which the contralateral hand would have to be used in the subsequent response. Taken together, our findings suggest that both the percept and the way in which it is processed downstream change as a function of prior probability.

Radoslaw M. Cichy and J.-D. Haynes

Decoding the what and where of object exemplars and categories across the hemifields

Theory and Analysis of Large Scale Brain Signals, Bernstein Center for Computational Neuroscience Berlin; Berlin School of Mind and Brain

Previous research in humans and monkeys has revealed contradictory findings about the functional organisation of the ventral visual pathway. Object sensitive cortex (LOC) may be both the site of position invariant object representation as well as retinotopically organized.

Here we studied whether object sensitive cortex contains position independent information about object exemplars across the visual hemifield as well as object-invariant position information. We used high-resolution fMRI of the ventral visual stream to measure response patterns elicited by 12 different objects, 3 for each of the 4 categories (animals, cars, chairs, places) presented either in the left or right visual hemifield. Each object presented either left or right of fixation was treated as a separate condition, allowing the analysis of the representational structure in LOC on exemplar level both within and between category boundaries. Multi-voxel pattern analysis was utilized to determine the amount of information about position-invariant object discrimination and object-invariant position discrimination in LOC. Furthermore, to describe the relationship between low-level visual similarity and category structure of LOC, we compared object discriminability in early visual areas and LOC for position-dependent object representation within and across category boundaries. We found that LOC contains hemifield-invariant object information both within and across category boundaries. Discrimination accuracy between objects across category boundaries proved to be significantly higher than within category boundaries. Although this effect was also evident in early visual areas when objects were decoded dependent on visual position, it proved to be significantly higher in LOC than in early visual areas. Furthermore, we found strong object-invariant position information in LOC.

Our results indicate (1) a widely distributed feature map structure of LOC organized by low-level visual similarity within category boundaries, (2) a category structure exceeding low-level similarity, and (3) a retinotopic organization based on receptive fields spanning both visual hemifields.

Carsten Bogler, S. Bode, and J.-D. Haynes

Two modes of perceptual decision making with and without awareness

Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig

Perceptual decision making depends heavily on the quality of sensory information. When an object is clearly visible we can effortlessly perceive it. But when it is hard to see we often believe to be purely guessing. Most models of decision making assume that perceptual decisions under high and low visibility are based on the same brain network. The trial-to-trial variability when subjects are guessing is believed to depend on noise fluctuations in the sensory system. Here, we used a combination of fMRI and multivariate pattern classification to test whether visibility has any effect on the signals that are used for decision making. As expected, we found that decisions regarding clearly visible objects are predicted by signals in sensory brain regions. However, when the objects were barely visible a different network outside the visual system became maximally predictive. This parietal region is known to be involved in free decisions, even when no sensory stimuli are involved. Thus, in contrast to standard models of perceptual decision making, the brain appears to switch to a separate symmetry breaking network when only insufficient sensory information is available.

POSTERS

Thursday, 10 December 2009

13.45–15.00 **odd numbers**

Friday, 11 December 2009

13.45–15.00 **even numbers**

Foyer of the Conference Center MDC.C

Francesco Boato, S. Hendrix , F. Hofmann, S. Djalali, L. Klimaschewski, M. Auer, I. Just, G. Ahnert-Hilger, and M. Höltje

P1

Enhanced regeneration and functional recovery after spinal cord injury by a peptidic fragment from Clostridium botulinum C_3

Cell Biology and Neurobiology, Charité – Universitätsmedizin Berlin

Rho-inactivating bacterial C_3 ADP-ribosyltransferases are commonly used biochemical tools to study mechanisms of neuronal process growth and regeneration. We identified a transferase-deficient region covering the amino acids 154-182 (C3bot154-182) responsible for the enzyme-independent effects exhibiting in vitro trophic effects on axonal and dendritic morphology of both cultivated cortical neurons and alpha motoneurons of the spinal cord.

Using organotypical slice cultures we also detected trophic effects of C3bot154-182 on length and density of outgrowing fibers from the entorhinal cortex (EC), and application of C3bot154-182 to EC-hippocampus co-culture significantly enhanced the re-innervation of the hippocampus by fibers of the perforant path.

In vivo, functional recovery and regeneration of corticospinal tract (CST) fibers following contusive spinal cord injury in mice was monitored after application of C3bot154-182. Single application of C3bot154-182 significantly improved locomotor restoration as assessed by Basso Mouse Scale and Rotarod treadmill. These data were supported by tracing studies showing an enhanced sprouting of CST fibers in treated animals. We also demonstrated an increased number of motor endplates in tibial muscles of treated animals after injury as well as a reduced proportion of non-innervated endplates.

Bruno Benedetti, C. Nolte, V. Matiash, and H. Kettenmann

Astrocyte-neuron interaction: chelation of astrocytic Ca^{2+} increases excitability in mouse barrel cortex neurons

P2

Cellular Neuroscience, Max Delbrück Center for Molecular Medicine Berlin-Buch

Electrical stimulation in barrel cortex layer 4 triggers neuronal and astrocytic cytosolic Ca^{2+} increase. While the neuronal Ca^{2+} signal spreads also across the barrel borders, the astrocytic response is delayed and restricted to the stimulated column (Schipke et al., *Cereb Cortex* 18:2450-9, 2008). We now addressed the question whether the astrocyte Ca^{2+} response has any impact on neuronal activity. To affect astrocytic Ca^{2+} signaling, we dialyzed these cells with 40 mM BAPTA using whole-cell patch clamp. We assume that BAPTA had spread via gap junctions into a network of astrocytes. After dialysis, L4 electrical stimulation still triggered Ca^{2+} responses in neurons. However, it completely inhibited Ca^{2+} responses in astrocytes within 100 ± 40 µm from the BAPTA injection site. Surprisingly, more distant astrocytes, which had not responded before, started to show Ca^{2+} responses to neuronal stimulation. We also patch clamped 31 granular and pyramidal neurons in the layers 3 and 4 of a barrel column. In control conditions, L4 electrical stimulation (30 pulses of 1 ms, 400 µA at 10 Hz) triggered a neuronal depolarization for 5.8 ± 2.7 s with trains of action potentials during the recovery phase. When the astrocyte Ca^{2+} signaling was suppressed, the same stimulation paradigm triggered multiple de- and repolarizing responses within a period of 12 s. Chronical depolarization by 20 ± 5 mV led to a repetitive spiking activity. In control conditions the spiking frequency decreased during the recovery phase following electrical stimulation. Astrocyte Ca^{2+} chelation prevented this decrease in the neuronal firing frequency. Our findings indicate that astrocyte activity in the barrel cortex has an inhibitory influence on the activity of L3 and L4 neurons.

Anna Lena Dätwyler, G. Michel, G. Lättig, U. Dirnagl, W. Paschen, M. Endres, and C. Harms

P3 Generation of two transgenic mouse models for the identification of neuronal SUMOylation-targets after stroke.

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

The posttranslational protein modification by members of the SUMO (*S*mall *U*biquitin-like *Mo*difier) 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. In stroke, levels of SUMO2/3 are dramatically increased in neurons, especially in regions of mild ischemia and the penumbra where cells are fighting for survival. A short duration of ischemia induces a state of tolerance which is sufficient to massively activate the SUMO conjugation pathway. We postulate that sumoylation is a conserved endogenous protective cell response induced under stress conditions. Specifically, we aim to elucidate the function of SUMO2/3 on neuronal cell fate after ischemic stress in vivo. Therefore, we are generating two transgenic mouse models through RMCE (recombinase-mediated cassette exchange) by targeted recombination into the silent Rosa locus. The transgenic animals will allow neuronal specific inducible gene expression of SUMO2/3 microRNA. Concomitant expression of Myc-tagged and silent mutated SUMO2 protein will rescue the phenotype caused by the miRNA and will additionally enable us to screen for sumoylation targets in vivo after stroke through tandem affinity purification (TAP) and a proteomics approach.

Odilo Engel, C. Meiel, J. Klehmet, and A. Meisel

Vagal influences on immunodepression following stroke

P4

Experimental Neurology, Charité – Universitätsmedizin Berlin

One of the major risk factors in stroke patients are infectious complications. Recently it became clear that CNS injury leads to a secondary immunosuppressive state which is mediated by the CNS itself over several pathways. There is an intense communication between the nervous and the immune system, and it was shown that both the hypothalamo-pituitary-adrenal axis and the sympathetic nervous system have a great influence in immunodepression following stroke. Recently another important way of brain-immune communication was uncovered: the cholinergic anti-inflammatory pathway, which is mediated by the parasympathetic nervous system and the vagus nerve.

In our results, vagotomy leads to a significant reduction in bacterial load in the lung, whereas stimulation with Nicotine leads to an increase in infectious complications in a mouse model of stroke. This suggests that the parasypathetic nervous system is also involved in the immunopathological events following stroke.

Andriani Fetani, M. Tsachaki, and S. Efthimiopoulos

P5 BRI2 protein homodimerizes via intermolecular disulfide bonds and none-covalent interactions

Institute for Anatomy, Charité – Universitätsmedizin Berlin

BRI2 is a transmembrane protein mutated in two neurodegenerative diseases, Familial British Dementia (FBD) and Familial Danish Dementia (FDD). These diseases have striking neuropathological similarities with the Alzheimer's disease. Cleavage of mutated BRI2 proteins by furin releases the amyloidogenic peptides ABri and ADan in FBD and FDD respectively, which accumulate as amyloid or preamyloid aggregates in the brain. There are two structural elements in BRI2 suggesting that homodimerization is possible. BRI2 contains within its transmembrane domain the GXXXG motif that has been shown to mediate homotypic protein interactions. Additionally, BRI2 bears a free extracellular cysteine residue (C89), which could mediate the interaction of two BRI2 molecules through an intermolecular disulfide bond. Our previous results have shown that BRI2 forms homodimers via disulfide bonds. In the present study, we sought to visualize the homodimers on cell surface; for this purpose we used the Bimolecular Fluorescence Complementation assay (BiFC). To investigate whether C89 mediates the homodimerization we mutated it to alanine. This exchange inhibited the formation of disulfide-linked dimers. Additionally, with co-immunoprecipitation experiments we found that non covalent interactions hold the BRI2 homodimers together even in the absence of disulfide bonds. Using BRI2 proteins with different deletions that also bear a mutation at C89, we discovered that the non-covalent interactions are formed in a specific part of the extracellular region of the protein. We conclude that BRI2 forms disulfide-linked homodimers through C89. Non-covalent interactions at the extracellular region are also involved in BRI2 homodimerization. The mutated BRI2 is a useful tool for the investigation of the normal homodimerization significance.

Emily Haines, V. Lang, V. Prinz, M. Balkaya, U. Dirnagl, and A. L. Pinar

Expression of pigment epithelium derived factor after cerebral ischemia

P6

Departments of Neurosurgery and Experimental Neurology, Charité – Universitätsmedizin Berlin

Pigment Epithelium Derived Factor (PEDF) is a multifunctional protein with therapeutic potential for the diseased nervous system. PEDF is widely expressed throughout fetal and adult tissues, including the adult central nervous system. Initially, PEDF was identified as an effective neurotrophic factor, further studies have shown that it also possesses multiple and varied biological properties, not only neurotrophic, but also neuroprotective, antitumorigenic, and potent antiangiogenic activity. In the eye, ischemic events underlie the progression of many diseases leading to blindness, including diabetic retinopathy, retinopathy of prematurity, macular degeneration, and glaucoma. PEDF has been shown to be upregulated in the eye in response to these ischemic events. Furthermore, application of PEDF has been shown to attenuate damage and exert a strong neuroprotective effects in retinal ganglion cells after ischemic reperfusion injury. We thus hypothesise that PEDF will be upregulated in the brain in response to ischemic stroke. We have used ELISA and immunohistochemistry to investigate the time course of PEDF protein expression following stroke, as well as to localise its expression to specific cell types and brain structures in the days following stroke. Here we show the upregulation of PEDF in response to stroke and localization to cell types of the CNS.

Rizwan U. Haq, A. Liotta, M. Jarosch, U. Heinemann, and C. J. Behrens

P7 Adrenergic modulation of stimulus-induced sharp wave-ripple complexes (SPW-Rs) in the adult rat hippocampus in vitro.

Cellular Mechanisms of Learning and Memory, Institute of Neurophysiology, Charité – Universitätsmedizin Berlin

Norepinephrine (NE) is an endogenous neurotransmitter distributed throughout the mammalian brain including hippocampus, where it, has been shown to reinforce the cognitive processes of attention and memory. Sharp waves-ripple complexes (SPW-Rs), which have been described in the rat hippocampus in vivo, are thought to be substantially involved in learning and memory by mediating the off-line processing and susequent transfer of declarative information from the hippocampus into the cortical mantle in a process of memory consolidation. Here, we employed the in vitro paradigm of hippocampal SPW-Rs to investigate the effects of NE (10–100 μM) on both the induction and expression of such network oscillations. We found that in the presence of both 50 and 100 μM of NE the stimulus induction of SPW-Rs was prevented. In addition, when NE was applied on established SPWRs, such activity was found to be reversibly blocked in both area CA3 and CA1. In more detail, we found that the unspecific β adrenoreceptor (AR) agonist isoproterenol (2 μM) as well as the β_1 agonist dobutamine (100 μM) significantly enhanced SPW-R activity. In contrast, SPW-Rs were significantly reduced by both α_1 and α_2 agonists, phenylephrine (100 μM) and clonidine (100 μM), respectively. Moreover, when the unspecific α AR anatgonist phentolamine (100 μM) was administrated, we observed an increase in both the SPW-R incidence and amplitude. Intracellular recordings obtained from both CA3 or CA1 pyramidal cells simultaneously recorded during SPW-R network activity revealed that the blocking effect of NE was accompanied by a pronounced hyperpolarization of about 5–10 mV in the majority of recorded neurons in both regions. Together, our data indicate that hippocampal SPW-R activity is effectively modulated by NE where the suppressive effects are mediated by α AR, and the facilitation of SPW-Rs is β_1-mediated.

Nicole Hentschel and F. Zipp

The role of α1,2-mannosidase in regulation of central nervous system inflammation

P8

Cécilie Vogt Clinic for Neurology, Charité – Universitätsmedizin Berlin

The presence of glycans at the cell surface plays an important role in the regulation of immune responses, and is implicated in inflammatory diseases. Our group recently showed that the glycosidase α1,2-mannosidase was upregulated in peripheral blood mononuclear cells of patients with multiple sclerosis (MS), but exclusively in those patients that showed the best clinical response to therapy with atorvastatin.

The α1,2-mannosidase leads to a shift from high-mannose glycans to complex glycans on the cell surface. To further investigate the role of this enzyme in central nervous system (CNS) inflammation, we used the drug kifunensine, which is a potent inhibitor of α1,2-mannosidase. When this drug was administered to mice, we showed a significant downregulation of complex glycans and an upregulation of high-mannose glycan, as revealed by binding to the fluorescent-congjugated lectins PHA-L and ConA, respectively. This effect was observed on dendritic cells and T cells, isolated from blood, spleen and lymph nodes.

We then immunized mice with myelin antigens to induce experimental autoimmune encephalomyelitis (EAE), an animal model of CNS inflammation used to study MS. Administration of kifunensine intraperitoneally during the induction phase of EAE led to a significant exacerbation in the clinical severity of the disease compared to mice receiving the control treatment. However, when kifunensine was administered at the peak of disease, no effect was observed.

These results suggest that inhibition of α1,2-mannosidase during the induction phase of CNS inflammatory disease has important consequences on the disease outcome. This underscores the need to consider α1,2-mannosidase, and other regulators of glycosylation, as important potential therapeutic targets for inflammatory diseases.

Dina Jezdic, D. Freyer, I. Przesdzing, A. Wunder, and U. Dirnagl

P9 The study of ICAM-1 expression after brain ischemia-reperfusion injury in vitro

Experimental Neurology, Charité – Universitätsmedizin Berlin

Intracellular adhesion molecule-1 (ICAM-1) was studied using the ischemia in-vitro model and tested on two endothelial cell lines, rat brain endothelial cells-6 (RBEC-6) and human microvascular endothelial cells (HBMEC). The RBEC-6 and HBMEC cell lines were exposed to 4 and 6 hours of oxygen glucose deprivation (OGD) following 5 and 3 hours (respectively) of reoxygenation to simulate ischemia/reperfusion in vivo. The cell lines were also exposed to 24 hours of oxygen deprivation (OD) following 5 hours of reoxygenation. The results were analysed by FACS and show that the expression of intracellular adhesion molecule-1 (ICAM-1) is dramatically (more than 12-fold) upregulated in RBEC-6 and HBMEC cell lines by an 18 hour exposure to the cytokine, TNF-α (25 ng/ml), but not when stimulated by OGD. 24 hours of oxygen deprivation alone showed increased ICAM-1 expression in HBMEC cell line but not in RBEC-6.

Julia A. Jira and P. A. Heppenstall

A domain of SLP_3 important for spatial, physical and functional interaction with ASICs

P10

Clinic of Anaesthesiology, Charité – Universitätsmedizin Berlin

In C. elegans a complex of proteins assembled at the membrane of sensory neurons accomplishes the task of transducing mechanical stimuli into electrical signals.

Mammalian homologs of these C. elegans proteins are members of the stomatin family as well as the acid-sensing ion channels (ASICs), both of which have also been implicated in mechanotransduction.

We have focussed on stomatin-like protein 3 (SLP_3) and identified a domain necessary for the interaction with ASICs in vitro. This N-terminal hydrophobic region is also important for the localization of SLP_3 to vesicular structures that are the major site of complex formation with ASICs as was observed by Fluorescence Resonance Energy Transfer (FRET) in living CHO cells. Moreover, the motility of these vesicles was found to depend on microtubuli integrity.
In order to assess the functional consequences of the SLP_3-ASIC interaction we performed electrophysiological experiments and could show that SLP_3 indeed influences ph-induced ASIC activity, but only when the N-terminal hydrophobic domain is present.

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

P11 Interaction of glioma cells with intrinsic brain cells

Cellular Neuroscience, Max Delbrück Center for Molecular Medicine Berlin-Buch

Gliomas are the most common primary tumors of the central nervous system. We are interested in studying the interactions of the glioma cells with microglia and stem cells. While the neural stem cells counteract glioma progression, microglial cells are pro-tumorigenic. In the present study, we plan to identify soluble factors and related receptors by which glioma cells communicate with brain cells. We therefore encapsulated glioma cells into a hollow fiber 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. 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, microglial cells and neural stem cells and combinations of theses cell types. All cell types they survived and even proliferated in the hollow fibers as studied with morphological and histological assays 1 to 20 days after encapsulation. Microglia co-injected into the fibers with glioma cells grow 3-dimensionally and fill the fibers lumen, whereas microglia alone adhered to the fiber wall. A three-dimensional arrangement of microglial cells could be accomplished by adding Matrigel when filling microglial cells into the fiber. In Matrigel, microglial cells acquired a more ramified morphology as compared to medium. We implanted the fibers into mouse brain and studied the brain tissue after 2 weeks. Neural stem cells and microglial cells accumulate around the fibers. Furthermore, microglia cells were found closer to the fiber as compared to s stem cells. Taken together, this approach will help us to identify factors by which these cell types communicate in an in vivo context.

Martha Maglione, O. Tress, B. Haas, K. Karram, J. Trotter, K. Willecke, and H. Kettenmann

Oligodendrocytes communicate to each other via gap junction channels formed by Cx47 and Cx32

P12

Cellular Neuroscience, Max Delbrück Center for Molecular Medicine Berlin-Buch

Increased genetic evidence revealed the importance of oligodendrocytic gap junction proteins in proper myelination function, since Cx32 or Cx47 mutations cause severe human myelopathies. According to previous studies oligodendrocytes in white matter exhibit gap junctions with astrocytes, but not among each other, while in vitro oligodendrocytes form functional gap junction channels. In order to understand the basis of the myelopathies caused by deletion or mutations of oligodendrocytic connexins, it is necessary to determine which of the connexins forms functional gap junctions in the central nervous system. We studied functional coupling among oligodendrocytes in acute slices of postnatal mouse corpus callosum. Using the patch-clamp technique we dialysed oligodendrocytes with biocytin, a gap junction-permeable tracer. On average 61 cells were positive for the tracer detected by biocytin labelling with Cy3-streptavidin. 77% of the coupled cells were positive for the oligodendrocyte marker protein CNPase, 9% for the astrocyte marker GFAP and 14% were negative for both CNPase and GFAP. This population of cells expressed NG2 (4%) and Olig2 (13%), markers for oligodendrocyte precursors. In Cx47 KO mice, the number of coupled cells was reduced by 80%, while lack of Cx32 or Cx29 did not affect coupling. Cx47-ablation completely abolished oligodendrocyte-astrocyte coupling. In contrast, in Cx43 KO mice, oligodendrocyte-astrocyte coupling was still present, but coupling to oligodendrocyte precursors was not observed. Oligodendrocytes in Cx32/Cx47 dKO mice were not coupled at all. We conclude that oligodendrocytes in white matter predominantly couple to each other dependent on Cx47 and Cx32 expression. In addition Cx47 contributes to the oligodendrocytes-astrocytes coupling.

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P13 The role of Arc/Arg3.1 in AMPA receptor trafficking and synaptic plasticity

International Graduate Program Medical Neurosciences

The effector immediate-early gene Arc/Arg3.1 is transiently expressed after synaptic activation and its mRNA is actively transported to stimulated dendritic regions. Arc/Arg3.1 is essential for the formation of long-term memory and for consolidation of synaptic plasticity such as long-term potentiation (LTP), long-term depression (LTD) (Plath et al., 2006) and homeostatic plasticity. Homeostatic changes in synaptic strength in response to altered synaptic activity are hypothesized to be mediated by interactions between Arc/Arg3.1 and dynamin 2 and endophilin 2/3, leading to endocytosis of surface AMPA receptors (AMPARs) (Chowdhury et al., 2006; Shepherd et al., 2006). However, it is not known whether different forms of plasticity depend on the same Arc/Arg3.1 mediated mechanism. To address this question, we investigated the effects of two distinct activity-inducing treatments on the regulation of synaptic and extra-synaptic AMPAR content. Whole-cell patch-clamp measurements of miniature excitatory post-synaptic currents (mEPSCs) after prolonged (48 h) increase or decrease of activity in vitro by application of bicuculline or TTX showed that both homeostatic up- and down-scaling of synapses is absent in Arc/Arg3.1-deficient mice. After a short-term global synaptic activation caused by kainic acid-induced seizures in vivo Arc/Arg3.1-deficient mice show increased mEPSC amplitudes and an elevated surface AMPAR content. This is in striking contrast to wild-type mice, which are able to actively maintain a constant AMPAR content despite the strong activation caused by seizures. Additionally, we show that dendritic localisation of Arc/Arg3.1 is important for the expression of these two forms of plasticity. We conclude that Arc/Arg3.1 is essential for up- and down-regulation of AMPARs after both acute and enduring activity-changes.

Anna Maslarova, A. Andrioli, C. Derst, R. Veh, and U. Heinemann

Voltage gated potassium channels in the epileptic mouse hippocampus make a difference

P14

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Potassium channels play a key role in controlling cell excitability. There is evidence that some types of epilepsies are associated with inherited and acquired channelopathies affecting potassium channels. Changes in potassium channel expression in the epileptic brain might profoundly influence the firing properties of neurons and contribute to establishment of chronic drug resistant temporal lobe epilepsy. Within the big family of potassium channels it remains to be determined which members are affected, in which neurons, in which region of the hippocampal formation, as well as their temporal pattern during epileptogenesis. Using immunohistochemistry we compared the expression of voltage gated potassium channels in the hippocampus and parahippocampal formation of kainate treated, chronically epileptic mice with that of controls, and observed a brand new pattern with over- and under expression of certain channels in different regions. The results are consistent with findings in the rat from immunohistochemistry and PCR experiments. Further electrophysiological experiments will aim on checking the impact of these morphological changes on the firing properties of neurons.

Ismini Papageorgiou, G. Eom, C. Huchzermeyer, R. E. Kaelin, F. L. Heppner, and O. Kann

P15 Microglia cell ablation in a transgenic mouse model. Electrophysiological properties

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Background: Microglial cells are central nervous system (CNS) glia that comprise brain's resident immune system (Davoust N et al., 2008). In the non-pathological brain, microglia exist at their 'resting' or 'surveying' state. It is characterized by a highly dynamic, ramified morphology and monitoring of the environmental activity (Inoue K et al., 2009; Yano S et al., 2004; Pocock JM and Kettenmann H, 2007). Upon detection of pathological conditions microglia respond with functional and morphologic changes hosted under the terminus 'activation' (Hanisch and Kettenmann, 2007).
Aim: We characterize an experimental approach whereby the role of resting state is investigated. Microglial cells are selectively deleted on adult mice in vivo and electrophysiological techniques are applied on acute brain slices.
Material and Methods: Conditional ablation is achieved by insertion of herpes simplex virus (HSV) thymidyl-kinase (TK) gene in BL6 mice under the promoter of CD11b (Heppner et al., 2005). FYI CD11b is a marker for macrophage lineage giving rise to microglia in the brain. In situ application of ganciclovir selectively induces apoptosis in CD11b-HSVTK expressing cells. We use recordings of local field potentials and changes in extracellular potassium concentration ($[K^+]_o$) in acute hippocampal slices to determine the effects of microglial ablation on neuronal functions.
Results/Perspectives: We have established a protocol to examine the following parameters: a) fast neuronal network oscillations as evoked by kainate, b) synaptic facilitation (paired-pulse index), and c) transient elevations in the extracellular potassium concentration ($[K^+]_o$) as induced by electrical stimulation. Our primary results argue upon slower K^+ kinetics of the microglia depleted hippocampus.

Julia Parnis, I. Sekler, H. Kettenmann, and C. Nolte

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

P16

Cellular Neuroscience, Max Delbrück Center for Molecular Medicine

Calcium (Ca^{2+}) plays an important role in many cell functions. In glial cells Ca^{2+} can enter the cell via store-operated Ca^{2+} channels (SOC). SOC are activated and open, when endoplasmic reticulum (ER) Ca^{2+} stores are depleted. This results in a high Ca^{2+} concentration ($[Ca^{2+}]$) close to the plasma membrane. Mitochondria in the vicinity of SOCs are thought to shuffle the Ca^{2+} away, thus preventing inactivation of SOC due to high $[Ca^{2+}]$. Recently, a Na^+/Ca^{2+} exchanger responsible for Ca^{2+} efflux from the mitochondria, NCLX, has been identified. (Palty, R. et al., submitted). The importance of NCLX for glial physiology has not yet been explored. Here, using immunoblot and immunohistology, NCLX expression was detected in mouse and rat brain lysates, in astrocytes of particular brain areas, and in primary murine microglia and astrocytes. Then, to study the subcellular location of the exchanger in astrocytes and microglia cell-fractionation experiments were performed on murine cultured cells. The results showed NCLX enrichment in mitochondria of astrocytes, while in microglia NCLX was found both in the crude ER and mitochondrial fractions. Next, to investigate NCLX influence on SOC entry in microglia, SOC were activated by chronic application of thapsigargin, and cytoplasmic Ca^{2+} was recorded. Inhibition of NCLX by the specific blocker CGP37157 resulted in a marked reduction of Ca^{2+} entry through SOC. If NCLX affects the major Ca^{2+} entry pathway, then its activity may affect also microglial Ca^{2+}-dependent functions, for example, LPS-triggered nitric oxide release. Indeed, pre-incubation of microglia with CGP37157 attenuated the release. In conclusion, our results indicate that NCLX is expressed in microglia and astrocytes, and its activity is important for microglial homeostasis and secretory function.

Steffen B. Schulz, Z. J. Klaft, U. Heinemann, and Z. Gerevich

P17 Effect of ATP-activated P2 receptors on hippocampal gamma network oscillations

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ATP is a well known energy supplier within cells and an extracellular signalling molecule acting at purinergic P2X and P2Y receptors. ATP receptors have been found in the hippocampus on principal cells, interneurons and glia. However, their functions in this region remain unclear. Therefore, we investigated 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). We found that ATP concentration-dependently reduced the power of both ACh- and KA-induced oscillations. Application of PPADS, a broad spectrum P2 receptor antagonist, reduced the power of ACh-, but not of KA-induced network activity. By using more specific antagonists we revealed that different ATP receptors have different effects on the ACh-induced gamma oscillations; while the blockade of ionotropic P2X receptors enhanced gamma power, antagonism of the metabotropic P2Y1 receptor inhibited it. By using ATP-sensitive electrochemical biosensors, we detected changes in the range of 1 to 5 μM during the onset of ACh-induced gamma oscillations. The next step will be to confirm these findings and to determine the basic level of [ATP] by a luciferin-luciferase assay. In conclusion, our results suggest that ACh and KA induce gamma oscillations by involving different neuron pathways either or not releasing ATP. The subsequent activation of P2Y and P2X receptors seem to have different modulatory effects.

Abdul Wahab, K. Albus, and U. Heinemann

Age and region dependent effects of antiepileptic drugs and bumetanide in immature rat temporal cortex

P18

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The incidence of seizures and epilepsy is highest in the neonatal period and gradually declines through childhood and then adolescence. It is well known that GABA has excitatory effect before the postnatal day 9 in rodents that contributes to enhanced excitability and ictogenesis in the developing rat hippocampus. In the present report, we have studied the effects of standard antiepileptic drugs (AEDs) on 4-aminopyridine induced tonic-clonic seizure like events (SLEs) in combined hippocampal-entorhinal cortex slices, which were prepared from Wistar rats between 3–10 days old (P4–10 group), and 14–18 days old (P14–18 group). Field potential recordings were carried out from CA3 and medial entorhinal cortex (ECm) of acute slices. AEDs such as valproic acid, phenobarbital, phenytoin and carbamazepine were used. In addition a possible contribution of depolarizing/excitatory GABAergic mechanisms to seizure like activity was analyzed by applying the inhibitor of NKCC1, bumetanide. The effects of AEDs were dependent on age, region and drug concentrations. Young group (P4–10) was relatively more resistant to AEDs than older group (P14–18). AEDs suppressed SLEs more significantly in ECm than CA3. In contrast, bumetanide, a NKCC1 co-transporter inhibitor, were more effective in blocking the SLEs in very young group (P3–5) and less effective in blocking the SLEs in group P6-10, whereas it could not significantly block the SLEs in any of the structure of older group (P14–18). Furthermore in contrast to AEDs, bumetanide suppressed the SLEs significantly in CA3 than those of ECm. We conclude that SLEs in the temporal cortex, in particular in CA3 and less so in the ECm, are resistant to AEDs during the first postnatal week. GABAA receptor activation, which induces depolarization/excitatory effects during the first postnatal week, contributes to seizure susceptibility and to the pharmacoresistance in the early postnatal temporal cortex.

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P19 Manipulating Alzheimer's disease by transgenic restriction of anti-Aβ antibodies to the periphery

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There is increasing evidence for an involvement of the immune system in neurodegenerative disorders such as Alzheimer's disease (AD). However, a clear dissection of the peripheral and/or central immune system's contribution to the pathogenesis of these diseases is still lacking. In this study, we aim to assess if anti-Aβ antibodies during Aβ immunotherapy exert their action (i.e., brain Aβ plaque clearance) in the periphery or within the CNS. We are in the process of generating transgenic mice that express the VDJ region of an anti-Aβ antibody (AB9) in an IgM expression construct (Heppner et al., 2001). This construct, which is based on the endogenous IgM promoter and enhancer, enables the expression of either a soluble or – by additional manipulation – a membrane-bound AB9 IgM by B cells. At least the membrane-bound form of AB9 IgMs will be expressed exclusively in the periphery, since B cells typically will not enter the brain. Upon pronuclear microinjection of the construct first potential founders are presently screened for integration of the transgene.

Anti-Aβ IgM expressing mice will be crossed to AD mice (APP/PS1) in order to test whether anti-Aβ antibodies lower amyloid plaque burden by acting as a "peripheral sink" (DeMattos et al., 2002). If this "sink hypothesis" is true, drugs can be designed that exert their action in the periphery and therefore minimize potential CNS-related side effects.

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The transcriptional activity of the forebrain of young and adult male zebra finches

P20

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The zebra finch has become a paradigmatic model system to investigate the neural and molecular control of auditory-guided vocal motor behaviour, adult neurogenesis and brain sexual dimorphism. Here, we report the first comprehensive map of the polyadenylated fraction of the transcriptome of the male zebra finch telencephalon at two ages, 50 days and 2 years after hatching. Using high-throughput next generation sequencing of paired end fragments, we detect over 50% of the annotated protein coding transcripts (ENSEMBL v.55) in the telencephalon at both ages and identify about 1,500 genes exclusively expressed in adult brains. Using the quantitative nature of the data we accurately estimate the relative expression levels of transcripts and found out that, e.g., genes differentially expressed between the juvenile and adult telencepahlon showed an enrichment in members of the Wnt signalling pathway, which is known to be involved in the process of vocal learning and adult neurogenesis. We exploited the information gained from the paired-end sequence reads and from reads falling onto splice junctions to provide an unprecedented view on transcript structures and alternative splicing in the zebra finch forebrain. Thus we identified more than 3,000 previously non-annotated alternative splicing events (ENSEMBL v.55). Our dataset further helped to refine 6,060 of the available ENSEMBL gene models by extending them in the 3'.

Daniel Beis, R. K. W. Schwarting, and A. Dietrich

P21 Classical transient receptor potential channel 6 and exploration behavior in BALB/c mice

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Non-selective classical transient receptor potential (TRPC) cation channels are important components in neuronal processes. For instance, TRPC6 is expressed in neuronal tissues, and shares important roles in differentiation, proliferation and axon outgrowth. To test the influence of TRPC6 on behavior, we analyzed a TRPC6-deficient (TRPC6–/–) mouse model in a BALB/c genetic background.

The health status and functional reflexes of wildtype and TRPC6–/– mice were tested by a modified SHIRPA-protocol, followed by three different behavioral paradigms for motor activity and anxiety-like behavior (marble defence burying test (MBT), open field (OF) and elevated star maze (ESM)). To investigate the cell-physiological function of TRPC6, PC12 cells (pheochromocytoma cells) were tested as a neuronal model. For this purpose, PC12 cells were differentiated by neuronal growth factor (NGF) treatment and the expression-patterns of TRPC1–7 were analysed. In wildtype and knock-out mice no physical abnormalities were detected in the modified SHIRPA protocol. Most interestingly, TRPC6–/– mice showed no significant differences in anxiety-like behavior in a MBT, but demonstrated reduced exploration and risk assessment in the OF and the ESM. Furthermore, a couple of old TRPC6–/– mice (> 180 days) presented pathological motor functions that may result from neocortical hypoxia and degeneration of Purkinje-cells in the cerebellum. Differentiated and undifferentiated PC12 cells expressed TRPC1, 3 and 7. After NGF treatment TRPC6 expression was elevated, although the amount of TRPC6 was lower than TRPC1. It is known that hyperforin (St. John's wort) activates TRPC6 channels (Leuner et al. 2007). Therefore, increased TRPC6 activity may also support exploration behavior as well as more vitality in depressive patients treated with hyperforin. But PC12 cells may not be an adequate model to investigate the function of TRPC6 in neuronal differentiation.

Yinth Andrea Bernal Sierra, L.-Y. Chiang, J. Hu, and G. R. Lewin.

Molecular characterization of gating springs for mechanotransduction in dorsal root ganglion neurons

P22

Molecular physiology of somatic sensation, Max Delbrück Center for Molecular Medicine Berlin-Buch

The ability to detect mechanical forces is a sense present in almost all organisms. However, of Aristotle's five senses, mechanotransduction alone still remains devoid of a clear understanding of its molecular basis. Genetic approaches in C. elegans and Drosophila have helped to develop a model for mechanosensation. In this model, a tether protein is linked to a channel complex (two DEG/ENaC pore forming subunits) and causes the channel to open after stimulation (1). Our laboratory has discovered this tether link in mammals using transmission electron microscopy (TEM) of sensory neurons cultured on laminin-1 (2). Electrophysiological recordings also show that after treatment of the cells with subtilisin, or when the neurons are cultured on a mix laminin-1/laminin-5, the tether protein disappears and mechanical sensitivity is abolished (3).

Six proteins have been selected as potential candidates for this tether protein and their expression pattern in DRG cells has been tested using immunofluorescence and microcontact printing using laminin-1 and a mix of laminin-1/laminin-5 (10:1). The molecular characterization of the tether will help to elucidate the apparatus necessary for mechanotransduction.

Regina Hartl and G. Lewin

P23 Identification of sensory neuron membrane proteins with a role in mechanotransduction

Molecular physiology of somatic sensation, Max Delbrück Center for Molecular Medicine Berlin-Buch

The sense of touch, pain and proprioception enables an organism to respond to physical stimuli such as pressure, temperature changes and stretch. In vertebrates sensory afferents of the trigeminal and dorsal root ganglia (DRG) terminate in the skin and other target tissues, where they transduce sensory stimuli into electrical impulses that are sent to the central nervous system. Little is known about the developmental mechanism by which sensory neurons in the DRG acquire mechanotransduction competence. Previous work of our laboratory unveiled the highly regulated process of mechanosensory acquisition which occurs in three distinct waves. While most nociceptive sensory neurons acquire mechanosensitive competence as a result of exposure to target-derived nerve growth factor, the process of mechanosensory acquisition in mechano- and proprioceptors is independent of neurotrophin-3 and may be driven by a genetic program. By using solexa based expression profiling we hope to identify molecules whose expression starts with the onset of mechanosensitivity and are required for sensory neuron mechanotransduction.

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Contribution of KCNQ5 to the medium and slow after-hyperpolarization currents in hippocampal neurons

P24

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Benign familial neonatal convulsion (BNFC) is a neurological disorder caused by mutations in the potassium channel genes KCNQ2 and KCNQ3, which contribute to the medium afterhyperpolarization current (ImAHP) and slow afterhyperpolarization current (IsAHP) in hippocampal neurons. KCNQ5 is not yet linked to any human disease but is broadly expressed in the brain similar to KCNQ2 and KCNQ3.

To investigate the role of KCNQ5 in the brain we generated a KCNQ5 dominantnegative (Kcnq5dn/dn) mouse. Histological analysis did not reveal structural brain abnormalities. Western blots of total brain proteins revealed that there is no detectable influence of the mutated KCNQ5 protein on overall KCNQ2, KCNQ3 and KCNQ5 levels. In addition, the subcellular localization of KCNQ2 and KCNQ3 is not altered in Kcnq5dn/dn mice. Using electrophysiological analysis we could show that KCNQ5 contributes to the ImAHP and IsAHP in a subset of hippocampal neurons where KCNQ5 is highly expressed. Therefore, our study is a direct demonstration that in addition to KCNQ2 and KCNQ3, KCNQ5 channels contribute to the ImAHP and IsAHP.

Maliha Shah, J. Bieschke, and E. Wanker

P25 Protein modifiers of α-synuclein-mediated aggregation and toxicity in Parkinson's disease

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α-synuclein (α-syn) – a key protein involved in Parkinson's disease (PD) – forms aggregates of amyloid fibrils that are toxic and cause the loss of dopaminergic neurons – a hallmark characteristic of PD neuropathology. Development of PD appears to be linked to processes that increase the rate of α-syn aggregation (Paleologou et al., 2005). Some proteins (e.g. Heat-shock proteins) interact with α-syn and interfere with aggregate formation, thereby providing a source for potential neuroprotective intervention. We utilize neuroproteomics-based, high-throughput, functional and aggregation assays to systematically screen a library of over 13,800 proteins, in vitro, in order to identify protein modifiers of α-syn aggregation. Proteins that significantly slow down aggregate formation are identified as potential inhibitors. The candidate proteins are then evaluated in a cell culture context (both yeast and mammalian) to determine their effect on α-syn aggregation and toxicity in vivo. In an effort to draw up a detailed, comprehensive, protein-protein-interaction network for α-syn, we also seek to identify proteins that modulate the modifier proteins themselves, i.e., 'second-stage modulators.'

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Microglia promote glioma cell invasion into brain tissue

P26

Cellular Neuroscience, Max Delbrück Center for Molecular Medicine Berlin-Buch

Glioblastoma multiforme is the most common and aggressive type of primary brain tumors in humans. They are highly diffuse and invade into healthy brain parenchyma, limiting the success rate of conventional therapies and almost invariably leading to the death of the patient. Microglial cells are the major immunocompetent cells of the brain controlling the innate and adaptive immune responses in the CNS. They accumulate within and around gliomas, forming up to 30% of the tumor mass. Microglia also promote tumor growth, thus in the absence of microglia, gliomas are smaller (Markovic et al., 2005). In the present study, we investigated whether microglia actively contribute to glioma invasion. We injected glioma cells into organotypic brain slices from mouse cortex. Stable transfection with EGFP allowed live cell imaging using 2-photon microscopy. By adding clodronate-filled liposomes to the brain slices for 24 h, we were able to deplete microglial cells from the slices without affecting the other cell populations (astrocytes, neurons and oligodendrocytes). We tracked individual glioma cells over a 400-min period and found that they migrated 0,0959 ± 0,0565 µm/min. Depletion of microglia resulted in a reduction of glioma cell migration to a mean of 0,066 µm/min ± 0,0364 µm/min. Thus, tumor-associated microglia promotes the invasion velocity of glioma cells in average by approximately 30%, an effect which is statistically highly significant (Mann-Whitney U-test, $p < 10^{-6}$). Moreover, tracing of individual cells over time revealed that the presence of microglia also increases the distances of glioma cells with respect to the point of injection. In conclusion, these observations provide evidence that glioma-associated microglia promote tumor cell invasion.

Grietje Tessmann, K. Färber, and H. Kettenmann

P27 Neurotransmitter modulate microglial functions

Cellular Neuroscience, Max Delbrück Center for Molecular Medicine Berlin-Buch

Microglia, the brain macrophages, represent the immune cells of the brain, which permanently scan the surrounding brain environment for any kind of physiological and pathological changes. Trauma, infection or ischemia trigger microglia activation and lead to changes in morphology, release of cytokines and NO, migration, proliferation and phagocytosis. We and other colleagues found, that microglial cells can actively sense neuronal activity by the expression of classical neurotransmitter receptors for GABA, dopamine, noradrenaline and serotonin. We found that the activation of these transmitter receptors results in a complex regulation of diverse microglial properties. Noradrenaline, but not dopamine attenuates the LPS induces IL6 and TNF-α release. In this project we studied the functional impact of neurotransmitters on microglial phagocytosis in two different slice models. We compared properties of invading, ameboid microglia during the early postnatal development with resting, ramified microglial cells in acute brain slices from adult mouse. We now show that norepinephrin, serotonin, dopamine and histamine attenuate phagocytosis activity to 70% as compared to control (unstimulated, 100%) in the invading, ameboid microglia cells, whereas glutamate and acetylcholine had no effect. These findings indicate that neuronal activity and the related release of neurotransmitter can have an impact on an important function of microglia, namely the regulation of phagocytosis.

Sven Dähne, N. Wilbert, and L. Wiskott

Learning complex cell units from simulated prenatal retinal waves with slow feature analysis

P28

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Spontaneous neural activity that spreads in waves across the retina, has been suggested to play a major role in prenatal self-organization processes that shape the visual system before the onset of vision. Recently, it has been shown that when employing sparse coding, these retinal activity patterns lead to basis functions that resemble optimal stimuli of simple cells in V1 [1].

Here we present the results of applying a coding strategy that optimizes for temporal slowness, namely Slow Feature Analysis (SFA) [4], to a biologically plausible model of retinal waves [3]. Previously, SFA has been successfully applied in modeling parts of the visual system, most notably in reproducing a rich set of complex cell features by training SFA with natural image sequences [2]. In this work, we were able to obtain complex-cell like receptive fields by training with image sequences derived from the retinal wave models. The obtained units are characterized by Gabor-patch-like optimal stimuli, sharp orientation tuning, and orientation invariance.

Our results support the idea that retinal waves share relevant temporal and spatial properties with natural images, and hence seem suitable training stimuli to shape the developing early visual system so that it is best prepared for coding input from the natural world.

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Vinzenz H. Schönfelder and F. A. Wichmann

P29 Machine learning in auditory psychophysics: System identification beyond regression analysis

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The identification the critical aspects ("cues") of the input stimulus on which observers base their decisions represents a main objective in psychophysics. Specifically in auditory experiments a number of cues are available to the observers. In general, comparing subject performance with ideal observers is not sufficient to determine the critical features, especially when subjects employ a combination of cues or switch cues. Recently, statistical algorithms from Machine Learning substantially assist psychophysics in quantitatively modelling and explaining behavior, providing a very powerful and flexible alternative to classical regression analysis. We propose a general approach that can be applied to very a broad class of auditory tasks: Using the outcome of psychophysical experiments, i.e., the sound stimuli as input and subject decisions as output, we train classification algorithms in order to mimic observer responses. When algorithm and observer show a similar behavior, we presume that the underlying decision mechanism may also be similar. Subsequently, this presumption will be directly tested. Here, we focus on the classical paradigm of tone detection in centered narrow-band noise. Despite a long history of research, no conclusive answer has yet been provided to the question, which cues observers rely on to solve this task. While experimental data is still being collected, we show in preceding simulations that a linear Support Vector Machine and Logistic Regression can indeed clearly discriminate between different observer strategies. Compared to classical linear regression, the reconstruction of employed cues is much more accurate and less biased by correlations between different features. Our simulations also provide an estimate on the amount of psychophysical data required for reliable analysis and interpretation.

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Microglia- and macrophage-specific IKK2 knock-out reduces survival rate after experimental stroke in mice

P30

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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 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 myeloid cells and microglia. 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 90% decrease of IKK2 mRNA 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, the inflammatory molecules such as NO and TNF-α were also found to be attenuated. Finally, we performed MCA occlusion for 60 minutes followed by 72 hours of reperfusion with these mutant mice. We observed a reduction of 25% of the survival rate in the knock-out mice compared to their 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, and H. Kettenmann

P31 Functional role of NTPDase activity for phagocytosis in microglial cells

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

Microglia cells represent the immune cells of the CNS and are of monocytic origin. Upon activation microglia cells acquire features of cytotoxic and phagocytic cells and take part in the remodeling of the nervous tissue following pathological insults. CD39, or NTPDase-1, is a microglia-specific ectoenzyme, which hydrolyses UTP, released from damaged tissue, preferentially to UDP (Zimmermann, 2006). UDP has been shown to facilitate phagocytosis in microglia mediated by P2Y6 receptor activation (Koizumi et al., 2007). In our study we analyzed the functional role of CD39 activity for microglial phagocytosis. To monitor the phagocytic activity of ramified microglia from adult mice and ameboid microglia from postnatal day 6 to 9, we applied fluorescent latex beads to acute brain slices comparing control and CD39 deficient mice. We quantified the incorporated particles by confocal microscopy and compared the results from CD39 KO and wild type mice. We found that ameboid and ramified microglia of CD39 deficient mice showed higher phagocytic activity as compared to the WT controls. Phagocytic activity in ameboid microglial cells from CD39 deficient mice was 72.5% and in resting ramified microglia 37.7% higher as comparing to the control. In control mice, UTP and UDP (600 µM) stimulated phagocytosis in ameboid microglia by 51.7% and 70%, respectively, and in resting microglia by 40.3% and 57.7%. In CD39 KO microglia of adult mice UTP and UDP led only to a stimulation of 15.7% and 38%, respectively. These data show that CD39 deficiency leads to the higher phagocytic activity of microglia and a decrease of the sensitivity to UTP or UDP with respect to stimulation of phagocytosis.

Uldus Khojasteh, M. Foddis, D. Harhausen, J. Koenig, U. Dirnagl, and G. Trendelenburg

Analysis of the functional relevance of the inflammasome in murine focal cerebral ischemia

P32

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Cerebral ischemia elicits acute inflammation which exacerbates tissue damage and is involved in secondary brain damage. A crucial part of innate immunity in the central nervous system involves production of proinflammatory cytokines, like interleukin (IL)-1β, mediated by inflammasome signaling. Caspase-1, an intracellular protease, cleaves the inactive precursors of IL-1β and IL-18 to yield active cytokines. 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 other inflammasome components. We determined whether ASC is expressed in the normal and postischemic brain. Mice were subjected to transient middle cerebral artery occlusion (MCAO). Results of our previous experiment showed that ASC mRNA is up-regulated in the affected tissue after focal cerebral ischemia. Immunohistochemical analysis revealed 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-1β 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 volume.

Sabrina Lehmann, D. Kaul, C. Krüger, F. Zipp, R. Nitsch, and S. Lehnardt

P33 Activation of TLR7 in microglia leads to neuroinflammation

Institute for Cell Biology and Neurobiology, Charité – Universitätsmedizin Berlin

The innate immune system is the first line of defense against various pathogens and requires the expression of Toll-like receptors (TLRs). In macrophages, TLR7 plays a crucial role in immune responses elicited by GU-rich ssRNA (i.e., ssRNA40) as well as synthetic antiviral chemicals, including imidazoquinoline components (i.e., imiquimod) and guanine nucleotide analogs (i.e., loxoribine). These compounds were initially described to activate mouse TLR7 and are potent immune response modifiers leading to antiviral and antitumor activities. Microglia serve as the major innate immune cells in the CNS. Employing PCR, in situ hybridization, and immunocytochemistry, we demonstrate that TLR7 is expressed in these cells. Incubation of microglia with all three of the above mentioned TLR7 ligands leads to activation of these cells displaying an ameboid shape and releasing inflammatory cytokines such as TNF-α and IL-1β. Real-time PCR analysis revealed that transcripts of the TLR downstream signaling molecules TRAF6, IRAK1 and IRAK4 were upregulated in response to activation of TLR7. In order to investigate the impact of TLR7 activation on neuronal injury in this context, co-cultures comprising cortical neurons and microglia derived from WT- and TLR7KO mice were incubated with the named TLR7 ligands. Subsequent analysis by immunocytochemistry and TUNEL staining showed that incubation with loxoribine and imiquimod induced neuronal cell death only in the presence of WT microglia. To investigate the role of TLR7 in an activated innate immune response in vivo, imiquimod and loxoribine were injected into WT and TLR7KO mice intrathecally. Instillation of both ligands caused an activation-like morphology of microglia in WT, but not in TLR7KO mice.

These data indicate a molecular relationship between viral infection, activation of the resident immune system in the CNS through TLR7, and neuronal injury.

Tina Leuenberger, V. Siffrin, J. Herz, M. Paterka, H. Radbruch, R. Niesner, and F. Zipp

Isolation and expansion of CD8 T cells with the potential to suppress encephalitogenic CD_4 T cells in vitro and attenuate EAE in vivo

P34

Cécilie Vogt Clinic for Neurology, Charité – Universitätsmedizin Berlin and Max Delbrück Center for Molecular Medicine Berlin-Buch

T cells are critical for the pathogenesis of multiple sclerosis (MS) and the animal model experimental autoimmune encephalomyelitis (EAE). However, the importance of different T cell subsets is highly controversial. CD_4+ T cells, mainly from the Th17 subtype, are essential mediators of the disease, whereas the contribution that CD8+ T cells have in EAE is not well understood so far. To investigate the regulatory potential of CD8+ T cells in chronic neuroinflammation, we isolated and expanded CD8+ T cells from C57Bl/6 mice showing remission in MOG induced EAE and tested their capacity to suppress encephalitogenic CD_4+ T cells in vitro. We further examined the effect of the presence of these CD8+ T cells on the clinical course of EAE and investigated their behaviour at the site of inflammation by life-time two-photon imaging in living anaesthetized mice. Whereas ex vivo CD8+ T cells from EAE-recovered mice showed no suppressive phenotype, the in vitro expanded CD8+ T cells suppressed encephalitogenic CD_4+ Th17 cells in vitro. When expanded and thereafter transferred into EAE-recipient mice before the onset of disease, the CD8+ T cells had a beneficial effect on the disease course. Life-time two-photon imaging in living anaesthetized mice showed that the transferred CD8+ T cells formed prolonged contacts with autoreactive CD_4+ Th17 cells within the CNS of EAE-mice compared to control CD8+ T cells, suggesting a cell-cell-contact dependent mechanism of suppression in vivo. Taken together, our results show that from the CD8+ T cells isolated from EAE-recovered mice, cells with regulatory potential can be expanded in vitro, which suppress encephalitogenic T cells and when used in a therapeutic approach in EAE attenuate the course of the disease.

Linn Lundvall, and R. R. Schumann

P35 IL-1β release during meningitis: Synergy of TLR and NLR stimulation

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Meningitis is a life-threatening inflammatory disease mainly caused by bacteria and viruses. The most common bacterial pathogens are Streptococcus pneumoniae (Gram-positive) and Neisseria meningitides (Gram-negative). Bacterial components such as LPS, lipopeptides or peptidoglycan (MDP, mesoDAP) can stimulate pattern recognition receptors (PRRs), i.e., Toll-like receptors (TLRs) that are transmembrane receptors of APCs, and Nod-like receptors (NLRs), located in the cytoplasm of a variety of cells. TLR stimulation by bacterial ligands causes translocation of transcriptional factor NF-κB into the nucleus and expression of the immature pro-inflammatory cytokine pro-IL-1β, whereas NLR stimulation induces cas-pase-1 activation, which is essential for processing pro-IL-1β into mature IL-1β and its secretion into the extracellular space.

We hypothesize a synergistic effect between TLRs and NLRs leading to increased release of mature IL-1β during bacterial meningitis infection in brain-derived cells in vitro and in vivo.

First results show an increase in IL-1β release in S. pneumoniae infected mice after 24 hours. In vitro studies revealed an increase in IL-1β levels after a costimulation with the ligands LPS, or lipopeptide (LP2) on one hand, and mesoDAP or ligand MDP on the other: In murine RAW 264.7 cells and primary murine astrocytes a synergistic enhancement of IL-1β release was observed. Western blot analysis of stimulated human astrocytoma cell line

U-87 lysate reveal a strong constitutive expression of cytoplasmic procaspase-1 and proIL-1β. When stimulated with LP2 and MDP, a strong active caspase-1 expression is observed but a weak cytoplasmic IL-1β expression, assuming that proIL-1β is cleaved by caspase-1 and mature IL-1β is released into the extracellular space.

First siRNA experiments show that a knock-down of nod2 followed by TLR and NLR stimulation lead to a diminished IL-1β release.

Mark-Christoph Medelin,[1] I. Ofek,[2] and R. R. Schumann[1]

Lipopeptide/Lipoteichoic acid (LTA) interaction with toll-like receptor 2

P36

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The family of toll-like receptors (TLRs) plays an important role in the innate immune response of the mammalian host against invading pathogens. Furthermore, intrinsic mediators may also trigger these receptors leading to an enhanced inflammatory response in numerous diseases. TLR2 has been shown to recognize cell wall fragments of different pathogens by forming heterodimers with either TLR1 or -6 as we and others have shown. Recently a controversy has been evolved concerning the ability of Lipoteichoic acid (LTA) to stimulate TLR2. Our working hypothesis is that monoacylated lipopeptides have the ability to form immunostimulatory dimers with diacylated lipopeptides after pre-incubation, while the single agents are inert. To this end we stimulated isolated human mononuclear cells as well as the murine macrophage cell line RAW 264.7 with lipopeptides that have been preincubated in order to form dimers. As readout TNF release of the cells was measured by ELISA. In the human system a modulatory effect of certain mono-acylated lipopeptides could be observed. However, interindividual variations depending on the donor occurred. Therefore we focused on the murine cell line in oder to confirm the results.
In a further step the HEK293 human embryonic kidney cell line transfected with TLR2 will be instrumental to confirm that the effects observed are TLR2-dependent. Finally, experiments will be performed with primary murine microglia and astrocytes obtained through cooperations within the Graduiertenkolleg. Elucidating the mechanism of TLR2 stimulation may lead to a better understanding of neuroinflammation.

Yvonne Schmidt and H. Machelska

P37 Effects of DAMGO on the discharges of primary sensory neurons in a neuropathic pain model

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We investigated the effects of peripheral μ-opioid receptor activation on mechanical thresholds and action potential discharges of primary sensory neurons in a mouse model of neuropathic pain. In a chronic constriction injury model of the saphenous nerve (CCS) we examined the effects of the administration of μ-opioid receptor agonist DAMGO on von Frey hair-induced mechanical thresholds and on nanomotor-induced repetitive mechanical stimulation in an in vitro skin-nerve model. Experiments were performed on isolated paw tissue from CCS-operated and sham-operated animals (both 2 weeks post surgery) or in animals without operation. Control experiments included the application of the μ-opioid receptor antagonist CTOP or the application of buffer solution. We found no difference in the baseline mechanical thresholds of different sensory fiber types from uninjured and injured saphenous nerves. Interestingly, the baseline action potential frequency of slowly-adapting sensory fiber types seemed to be lower in injured nerves compared to those from uninjured nerves. In the injured nerves about 30–40% of Aδ and C fibers, but not Aβ fibers, were DAMGO-sensitive, resulting in an increased mechanical threshold and a decreased number of action potentials after DAMGO administration to their receptive fields. These effects were reversed by CTOP, indicating a selective μ-opioid receptor-mediated action. Furthermore, C fibers from injured nerves had a lower action potential frequency after administration of DAMGO; an effect that was not seen in fibers treated only with the buffer solution. Our results suggest that peripheral μ-opioid receptors can be directly activated in cutaneous C and Aδ fibers to diminish their excitability after nerve injury.

Stefanie Seifert, K. Färber, W. Uckert, and H. Kettenmann

Expression of a calcium sensor protein in microglia in vivo

P38

Cellular Neuroscience, Max Delbrück Center for Molecular Medicine Berlin-Buch

Microglial cells express a variety of receptors which are linked to calcium signalling via release from internal stores or by entry through the cytoplasmic membrane. We have previously studied microglial calcium signals in vitro using calcium sensitive dyes, but so far calcium signals in microglial cells in situ could not be analyzed, since no procedure to load the cells with calcium indicators has been found yet. To overcome this restriction we have created two retroviral constructs containing GFP or the calcium sensitive construct GCaMP2 [Tallini et al., *PNAS*, Vol. 103 (2006), 4753–8]. The GCaMP2 retroviral construct was tested by transduction of primary microglial cells. 24 and 48 h after infection we recorded fluorescence increase in response to ATP. To test the construct in vivo, we induced a stab wound in the cortex of aduld mice to trigger microglial proliferation. Two days later, retroviruses were injected into the same site. First GFP-retrovirus was injected and GFP positive cells were identified at day 3, 6, 21 and 42 by Iba-1 staining. Membrane current recordings of day 3 and 6 revealed, that the cells expressed the current pattern of activated microglia characterized by inactivating inward currents and non-inactivating outward currents. 42 days after injury the membrane current pattern was closer to ramified microglia, which are typically characterized by a lack of these membrane currents. To analyze microglial calcium signals we transduced the GCAMP2-retrovirus applying the same procedure as described above 24 h after transduction, we prepared acute brain slices and recorded fluorescence increases in cells close to the lesion site in response to ATP. We conclude that the retroviral vector approach in combination with a stab wound can be used to study calcium signalling in microglial cells in a brain tissue environment.

Gürsel Çalışkan and U. Heinemann

P39 Place cell recordings in an odor-associated Y maze task

Neurophysiology, Charité – Universitätsmedizin Berlin

How we learn and, subsequently, form memory representations in our mind has been one of the main questions of neurosciences. Discovery of hippocampal place cells, which fire selectively when a rat occupies a particular location, has led scientists to further understand the underlying cellular mechanisms involved in spatial learning. Moreover, behavior-dependent field activity in different frequency ranges such as theta (4–10 Hz), gamma (30–80 Hz) and sharp waves (1–3 Hz) which are superimposed to high frequency oscillations (120–250 Hz) (SPW-R) also been long studied. Odor learning in rats has widely been used as a model to study learning and memory in rodents. In this study, rats have been trained in an-odor discrimination task in a Y maze while single unit recordings and corresponding EEG recordings from CA1 region of the hippocampus were performed. After application of an odor in a start box, which signals that the food reward is on the left or the right side of the Y maze, the door between the Y maze and start box was opened and the rat was free to choose an arm. The reward was given at the end of the arm if the rat chose the correct odor-arm combination. After 10–15 trials the rat was put in a sleeping cage where the activity in CA1 region was recorded during resting period. After baseline recording during sleep, during which SPW-R dominate the main field activity, one of the odors that was used during training was applied into the sleeping cage to see whether any alteration in unit activity and SPW-R activity occurs, and if yes, whether the behavior is faster improved in those animals where the odor was applied compared to the control animals. Preliminary findings fail to find any change in ripple activity after odor application. However, further analysis needs to be performed to see whether place cell activity during SPW-R is altered.

Silvia Fano and U. Heinemann

Effects of Astemizole on rat hippocampal network oscillations

P40

Neurophysiology, Charité – Universitätsmedizin Berlin

The mammalian hippocampus displays a variety of neuronal network oscillations, which are related to different functional states. During active wakefullness and spatial exploration theta (~5–15 Hz) and gamma (~30–100 Hz) rythms dominate. These network oscillations are necessary for retrieval and storage of information.

The aim of this work is to test the effect of Astemizole, an histamine H1-receptor antagonist and Kv 11.1 blocker on oscillatory activity at gamma frequency.

Experiments were performed on horizontal hippocampal slices obtained from brains of young adult Wistar rats (~160 g). Kainic acid, continuosly bath applied at a concentration of 100 nM was used to induce gamma oscillations. Gamma oscillations were extracellulary recorded from 'stratum pyramidale' of area CA1 and CA3b.

Preliminary results show that Astemizole significantly increased the power by about 40% of gamma oscillations at a concentration of 5 μM. When the concentration of Astemizole was increased to 30 μM the power was even more increased by 80%, while Astemizole applied at a concentration of 1 μM had no significant effect. Interestingly, Sertindole, another Kv 11.1 blocker, at the concentration of 5μM didn't change the power of gamma oscillations, while Quinidine, a Kv10.1 and 10.2 blocker, applied at a concentration of 10 μM led to a reduction of gamma oscillation power. Therefore, we hypothesize that the influence of Astemizole on gamma oscillations is due to the block of H1 receptors. This hypothesis is tested by applying fexofenadine, another antihistaminergig drug. I will further test whether Astemizole and other Kv11 blockers affect the induction and incidence rate of sharp waves ripple complexes.

Stephanie Wegener, P. Beed, and D. Schmitz

P41 Presynaptic kainate receptors depress synaptic transmission in the medial entorhinal cortex

Neuroscience Research Center, Charité – Universitätsmedizin Berlin

The medial entorhinal cortex (mEC), a part of the parahippocampal formation, is pathophysiologically involved in the initiation and propagation of temporal lobe epilepsies. Epileptic seizures specifically harm pyramidal cells in the mEC layer III; they can be induced experimentally by the injection of kainate (KA), an agonist at kainate-type glutamate receptors (kainate receptors, KARs). To date, not much is known about the function of KARs in mEC layer III pyramidal cells. Performing whole-cell patchclamp recordings in mouse hippocampal brain slices, we show that low doses of KA depress excitatory synaptic transmission to these neurons.

In accordance with observations in other brain regions, we determine a presynaptic locus of KA action. Our data suggest that the probability of glutamate release onto mEC layer III pyramidal cells is lowered by KA via a calcium-dependent mechanism. That is in line with evidence recently accumulating that KARs may be capable of nonionotropic signalling. We further aim to identify the KAR subunit(s) mediating the synaptic depression as well as the physiologic context, in which this depression might occur.

Nikos Green, G. Biele, and H. R. Heekeren

Trading off accuracy and speed for reward maximization in perceptual decision making

P42

Neurocognition of Decision Making, Max Planck Institute for Human Development; Affective Neuroscience and Psychology of Emotions, Freie Universität Berlin

In reaction time tasks, decision makers select an action from a set of alternatives. They determine rewarded choices by collecting evidence until a point of choice, thus either making decisions quickly, thereby risking more errors, or making decisions carefully, thereby risking to have fewer opportunities for being rewarded. Electrophysiological studies in monkeys have shown that cortical and striatal brain regions are involved in this Speed-Accuracy Tradeoff, however their interaction remains unclear. Computational models suggest a modulation of the coupling between striatal and cortical neurons as the mechanism by which decision makers adapt their behavior to optimize reward rate. To investigate this hypothesis and the role of reward in it, we used an fMRI design, in which participants performed a 2 alternative forced choice random motion dots task in blocks. Blocked rewards emphasized either accuracy, or speed, or both. Participants had to trade off speed and accuracy to obtain the maximal reward. Assuming that participants' behavior is well described by a sequential sampling model of decision making, they could maximize their overall reward by modulating the amount of accumulated information for each decision. Results show a significant effect of reward condition on reaction time and a trend for percent correct (speed < both < accuracy). Imaging results reveal significant activation in several brain regions (during the decision phase) including the left dorsolateral prefrontal cortex and the cerebellum. We use these regions in a functional connectivity analysis and find a significant modulation of the coupling of striatal regions to them when comparing the different reward conditions. Our results suggest that depending on the prevailing optimal strategy, reward optimization is achieved by modulating the coupling between involved brain regions.

Christoph Korn, T. Sharot,* and R. Dolan*

P43 How do we maintain optimism?

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A positive learning bias and its neural correlates. A large body of literature demonstrates that humans show a pervasive optimism bias; paradoxically they expect their personal future to be more positive than it actually turns out to be. How can people maintain overly positive views of their future although they frequently encounter information that challenges optimistic beliefs? We collected functional magnetic resonance imaging (fMRI) data while participants estimated their personal likelihood of experiencing 80 different negative life events such as having cancer, getting a divorce, or being robbed. To mimic the encountering of adverse information, participants saw the actual probability of how likely these events are to happen to an average person in the Western world after each of their own estimates. They then were asked to estimate their personal likelihoods for all events a second time. When participants initially underestimate the probability of a negative event happening to them, i.e., when they are optimistic for a given event, they update their estimates less than after an initial pessimistic overestimation. Intriguingly, the deviation between the first estimate and the population-based actual probability largely predicts the update in participants' beliefs when they start off pessimistic. For optimistic predictions, this is not the case. The anterior cingulate cortex (ACC) and the dorso-lateral prefrontal cortex (dlPFC) are commonly related to cognitive control and contextual monitoring. In the present study, fMRI signals in the ACC and the dlPFC differentiate between optimistic and pessimistic estimations, when participants see the average probability of a negative event happening to them. Humans seem to update their expectations by selectively incorporating information that enforces optimism, which may be mediated by cognitive control mechanisms implemented in the ACC and the dlPFC.

Ida Momennejad and J.-D. Haynes

Remembering the future: Decoding the what and when of prospective Intentions

P44

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Prospective memory (PM) refers to the timely remembering of a planned future action (e.g., attend a meeting, at 15 p.m.). This requires one to successfully a) encode, b) maintain, and c) retrieve two intention components: what and when. In event based PM an external event marks the when of retrieval and initiation of intended action, e.g., drive as soon as lights turn green. In time-based prospective memory on the other hand endogenous time/duration estimation triggers self-initiation of the intended action, e.g., check the oven in 20 minutes while reading a book.

In time-based prospective memory, in absence of external triggers of action, it is not well known where the brain maintains the information concerning the intended action and keeps track of their execution time. This question becomes more pressing with increase in maintenance duration (i.e., longer than a couple of seconds) and/or an increase in the demand of different tasks we perform during the delay. In a time-based PM neuroimaging paradigm, we were able to successfully decode the What and When of prospective intentions using multivoxel pattern classification on fMRI data. We were able to retrieve information concerning the a) prospective task, and b) the prospective duration with high decoding accuracies during different phases of the time-based PM paradigm.

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P45 Is the gain worth the pain? – The willingness to suffer for monetary gain

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In everyday situations, we usually face options that have more than one dimension. Each dimension 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 different dimensions are converted into a single internal common value currency to facilitate the comparisons of the valuation of diverse future behavioral acts or stimuli, thereby enabling successful decision making. This common value currency of an option can be referred to as the subjective value, incorporating individual weighting of each dimension.

The goal of the present study is to examine the neural representation of such integrated subjective values and the decision-making mechanism underlying choices among multi-dimensional options. We investigated 23 healthy male subjects using functional magnetic resonance imaging (fMRI) while they chose among multi-dimensional options. Each option consisted of physical pain (electrical pulse) and monetary gain. Crucially, subjects received both the amount of money and strength of pain of the chosen option.

Different sub-regions of the prefrontal cortex correlated with the magnitude of money and the severity of pain, respectively. Furthermore, we fitted individual behavioral data to economic models simulating the cost benefit integration to estimate the subjective value for each complex option. Using these subjective values, we demonstrate that the medial prefrontal cortex codes the integrated subjective value.

Anne Beck,[1] F. Schlagenhauf,[1] L. Deserno,[1] T. Wüstenberg,[1] J. Hein,[1] T. Kienast,[1] T. Kahnt,[1] K. Schmack,[1] C. Hägele,[1] B. Knutson,[2] J. Wrase,[1] and A. Heinz[1]

Ventral striatal activation during reward anticipation correlates with impulsivity in alcoholics

P46

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Background: Alcohol dependence is often associated with impulsivity, which may be correlated with dysfunction of the brain reward system. We explored whether functional brain activation during anticipation of incentive stimuli is associated with impulsiveness in detoxified alcoholics and healthy controls.
Methods: 19 detoxified male alcoholics and 19 age-matched healthy men participated in a functional magnetic resonance imaging (fMRI) study using a monetary incentive delay task (MID), in which visual cues predicted that a rapid response to a subsequent target stimulus would either result in monetary gain, avoidance of monetary loss or no consequence. Impulsivity was assessed with the Barratt Impulsiveness Scale (BIS-10).
Results: Detoxified alcoholics showed reduced activation of the ventral striatum during anticipation of monetary gain relative to healthy controls. Low activation of the ventral striatum and anterior cingulate during gain anticipation was correlated with high impulsivity, significantly in alcoholics and at a trend level in controls.
Conclusions: This study suggests that reduced ventral striatal recruitment during anticipation of conventional rewards in alcoholics may be related to their increased impulsivity, and raise questions about whether this dysfunction might respond to treatment.

Philipp Bode

P47 The view of the other one – An analysis of structure and genesis of perspective pluralism in the philosophy of mind

Volkswagen Foundation Research Project "The brain as an organ of interrelations," Institute of Philosophy, Humboldt-Universität zu Berlin

In the context of 'perspective pluralism' as an epistemic explanation strategy in the philosophy of mind the second person perspective has became popular far beyond the inner circles of philosophy. But the term "second person perspective" seems meaningful only in a metaphorical sense; in addition it may seem inconsistent in some way. What is even more, the term second person perspective has undergone a severe change in the course of history.

The project is divided into three parts: The historical part examines the philosophical and genesis of central terms and figures in the history of science. These terms and figures form the basis for the perspective pluralism. The systematic part examines the logical, grammatical and epistemological foundations of the idea of the perspective pluralism. The pragmatic part finally will uncover the actual meaning of the second person perspective, its precise use and its ethical context.

The project is part of a larger research project of the Volkswagen Foundation. Another part of this Volkswagen project is work of Marisa Przyrembel (who is also presenting a poster).

Marc Borner

Subpersonal conditions of self-consciousness

P48

Institute for Philosophy, Humboldt-Universität zu Berlin

Within the proposals to explain consciousness one can classify in theories, which go under a reflexive approach and theories that go under a non-reflexive model. Reflexive theories of self-consciousness explain self-consciousness as being constituted via a reflexive process, in which the self reflects on itself. Several problems could be mentioned regarding these approaches. A very obvious one is elucidated if one asks, how this first self that is able to reflect, is itself being constituted. We get into an infinite regress.

Theories that try to overcome this vicious circle are found within so called non-reflexive approaches. One of these approaches is it to assume the existence of a level before every reflection: a so called pre-reflexive self. This level is constitutive for every reflection but is not itself evolved from a reflexive process.

Theorists in Germany from some thirty years ago, mainly Dieter Henrich and Manfred Frank (the Heidelberger Schule), tried to elucidate this phenomenon more clearly and also succeeded to great lengths. Nevertheless they were giving an outright negative definition: self-consciousness could not be understood as being the result of an intentional process. It could not be described as a case of identification. There are not two different poles. It is no kind of knowledge, it is no explicit reflection. Allover they claimed the phenomenon as not being further analyzable.

In my Ph.D. project I assume that the latter assumption can be expanded and one can analyze the phenomenon further, also giving a positive definition of this pre-reflexive level. I have the thesis that this can be reached by looking into empirical studies of self-consciousness that analyze a sub-personal level (like, e.g., Antonio Damasio did them). The fields of neuroscience, psychology and psychiatry I reckon can give fruitful and new insights into this old phenomenon and thus lead to a more clear concept of a pre-reflexive self and self-consciousness in general.

Doreen Braun, E. K. Wirth, and U. Schweizer

P49 Developmental expression of thryoid hormone transport proteins in the mouse brain

Institute for Experimental Endocrinology, Charité – Universitätsmedizin Berlin

Mutations in the gene encoding monocarboxylate transporter 8 (MCT8) lead to Allan-Herndon-Dudley-Syndrome (AHDS), an X-linked mental retardation syndrome. Patients suffer from severe psychomotor retardation, inability to speak, axial muscle weakness and little mental development after several months of age (Schwartz et al., 2007). MCT8 is a specific thyroid hormone transporter expressed in neurons and brain microvessels.

Surprisingly, mice deficient in Mct8 did not show the neurodevelopmental phenotype. We, therefore, assumed that other thyroid hormone transporters expressed in the mouse brain may compensate for the defect of Mct8 function. One candidate transporter is the L-type amino acid transporter 2 (Lat2, Slc7a8), that is known to transport neutral amino acids such as leucine, isoleucine, glycine and alanine (Segawa et al., 1999) as well as thyroid hormones (Friesema et al., 2001).

We have shown that Lat2 is significantly expressed in primary cortical neurons isolated at the time point when corticogenesis is in full progress in the mouse. In contrast, there is rather low LAT2 expression in developing human neurons. At this time, it appears as if MCT8 is the critical thyroid hormone transporter during human brain development. Only in the adult, LAT2 expression increases (Wirth, Roth et al., 2009).

Here, we present data on the distribution of Mct8, Lat2, and Lat1 (Slc7a5) in the developing mouse brain and in different cell types within the brain. Based on the hypothesis that Lat2 may compensate for loss of Mct8 function in the developing mouse brain, we are analyzing the phenotype of Lat2-deficient mice. Although we demonstrated the inactivation of Lat2 function, no neurological symptoms in Lat2-deficient mice are apparent. We are now generating mice deficient in both Lat2 and Mct8.

Hannah Bruehl and H. R. Heekeren

Brain atrophy and cognitive impairment in adolescents with type 2 diabetes mellitus

P50

Affective Neuroscience and Psychology of Emotions, Freie Universität Berlin

In the past three decades, obesity rates in children and adolescents have nearly tripled with a concomitant rise in type 2 diabetes mellitus (T2DM), which is etiologically linked to obesity. T2DM is a metabolic disorder characterized by insulin resistance and hyperglycemia, which in it's later stages or when poorly-controlled, is associated with multiple complications. There is an emerging literature suggesting that the brain may be a site of complications among elderly individuals with T2DM, manifesting as cognitive impairment and brain structural changes, and that this may be partly independent of occlusive cerebral vascular disease. Specifically, declarative memory and on the neural level, the hippocampus appear to be particularly affected by T2DM.

To date, there are no reports evaluating either cognitive performance or the impact of the disease on brain integrity in adolescents or young adults with T2DM. We therefore evaluated 18 obese adolescents with T2DM and contrasted them with 18 obese adolescents without any indication of insulin resistance on neuropsychological test performance (IQ, psychomotor speed, declarative memory, working memory, executive function, academic achievement) and brain volumetrics. We found that adolescents with T2DM showed descriptively reduced scores on all neuropsychological tests, with statistically significantly worse performance on IQ, tests of verbal memory and psychomotor efficiency. In addition, adolescents with T2DM had significantly smaller hippocampal and total prefrontal volume as well as increased global and prefrontal atrophy. We conclude that the brain is adversely affected early on by T2DM, independent of obesity and occlusive vascular disease.

Miriam Heydt, S. Amasheh, T. Grobosch, and C. Stein

P51 New sensitive LC-MS/MS method for quantification of a novel pain relieving drug: Analyses of intestinal transport mediated by absorption enhancers

Department of Anesthesiology and Operative Intensive Care Medicine, Charité – Universitätsmedizin Berlin, Campus Benjamin Franklin

In a series of models for acute and chronic inflammatory pain, the new morphine derivate AS006 (SANOCHEMIA Pharmazeutika AG Austria), has been shown to have excellent efficacy. The activation of central μ-opioid receptors is associated with adverse actions, including respiratory depression, sedation and physical dependence. However, experimental and clinical studies have shown that pain relief mediated by opioids does not exclusively take place in the central nervous system, but also occurs in the periphery. This implicates the importance of new opioids which do not have the ability to cross the blood brain barrier. In vivo experiments have shown that AS006 is an effective opioid with a selective peripheral site of action. Therefore, AS006 is an analgesic drug of high interest to be administered orally.

To increase the oral pharmacokinetic profile of AS006 we used the absorption enhancer chitosan. Chitosan decreases the paracellular resistance of epithelial cells by opening the tight junctions (TJ) via interaction between the positively charged amino groups of chitosan molecule with the negatively charged surface proteins of the TJ. Intestinal cells were grown on permeable supports and mounted in Ussing chambers, which were filled with HEPES buffered Ringer's solution. We developed a new liquid chromatography-tandem mass spectrometry (LC-MS/MS) method for the determination of AS006 in HEPES buffered Ringer's solution. AS006 was added to the apical side and opening of the paracellular pathway was induced by addition of chitosan. Samples were taken from the receiving (basolateral) side. An increased permeability induced by chitosan and increased oral absorption of AS006 may be a great benefit in future pain management.

Lena Kästner

A historical perspective on models of the mind & Why we still don't know what cognition is

P52

University College London, UK

Most contemporary cognitive scientists want to understand how the mind works; and what the mind does is commonly called "cognition." But what is cognition?

The dominant conception seems to be that cognition is a process eliciting cognitive phenomena in response to changing environmental and/or bodily conditions – where the behavioristic gloss is no accident. However, this does not give us a full-fledged theory of the cognitive; it does neither tell us what is distinctive about cognition, nor how cognition works or where to find it.

My project here is a modest one. Progressing through the history of cognitive science and its contributing disciplines, I will introduce various approaches to cognition. I will find that while we still do not know what is distinctive about the cognitive, we are essentially asking the very same questions that already bothered early psychologists: (1) Does our subjective experience make something count as cognitive that otherwise would not?, (2) Are body and environment causally relevant (in a non-trivial sense) or constitutive to cognitive processing?, and (3) What is implementationally and/or formally characteristic of cognition?

I will not defend a particular view. Instead, I claim that answering the above questions – and thus finding out what cognition is – will require us to specify a mark of the cognitive, viz. a criterion to distinguish cognitive from non-cognitive. Problematically, however, we do not even know what this criterion is supposed to look like; for we do not know whether "cognition" is a natural kind term, cluster term, or an umbrella term. I suggest giving priority to this consideration may be useful.

Dorit Kliemann, I. Dziobek, A. Hatri, J. Baudewig, and H. R. Heekeren

P53 "Schau mir in die Augen, Kleines:" Amygdala's role in reflexive orienting on emotional faces in autism spectrum conditions

Affective Neuroscience and Psychology of Emotions, Cluster of Excellence "Languages of Emotion," Freie Universität Berlin

When processing faces, subjects on the autism spectrum (ASC) focus less on the eyes than typically developed controls (NT). A 2-component model (Spezio et al., 2007) suggests that ASC specific gaze patterns on faces might reflect both an avoidance of and a missing orientation to eye contact. On the neural level, reflexive orientation to the eyes in NT is reflected by an increase of amygdala activity (Gamer & Büchel, 2009), whereas findings about amygdala activation and face processing in ASC remain contradictory.

We tested whether ASC fail to orient to the eyes, accompanied by a decrease of amygdala activity and whether ASC show a tendency to gaze away from the eyes, accompanied by an increase of amygdala activity.

Using fMRI and an eye tracking system, we monitored participants while they performed a facial emotion-discrimination task, in which fearful, happy, and neutral faces were presented for 150ms such that fixation started either at the eyes or the mouth.

ASC showed a reduced orientation towards the eyes and a decrease of amygdala activation whereas NT clearly oriented towards the eyes, accompanied by an increase of amygdala activation. When starting fixation on the eyes, ASC showed a strong tendency to gaze away from the eyes. The corresponding greater response in the amygdala is in line with the aversion component. The current results emphasize the specific role of the amygdala in adequately processing social information via mediating orientation towards social cues.

M. Olszanowski,[1] A. Szmalec,[2] Zuzanna Kłyszejko,[1] and T. Rutkowski[1]

Control of interference in dual-tasking – Does conflict monitoring theory account for the control mechanism in dual-task?

P54

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[2] Department of Experimental Psychology, Ghent University

The current study investigates the mechanisms underlying the control of interference during dual-task coordination. Partially inspired by the Conflict Monitoring Hypothesis (Botvinick et al., 2001), we test the assumption that interference during dual-tasking is resolved by a top-down adaptation mechanism which is responsible for behavioral adjustments in the prioritization of the coordinated tasks. In a series of two experiments, we provide evidence for the operation of such an adaptation mechanism by demonstrating that the amount of dual-task interference is a function of the probability of previously encountered single- versus dual-task events. In Experiment 1 we investigate if the same executive function is present in a conflict task, as a Stroop task, as in a dual task. This was done by manipulating the probability of interference in both tasks. The goal of Experiment 2 was to extend the results from Experiment 1 to a dual task with a memory task as a primary task. We wanted to explore if interference and probability effect are similar when participants have to be continuously processing information. We conclude that dual-task interference shows strong similarities to the so-called Stroop-like types of cognitive interference in the way suboptimal performance is dealt with by the cognitve system.

B. Bonakdarpour, Sladjana Lukic, K. Garibaldi, D. den Ouden, and C. K. Thompson

P55 Posterior perisylvian lesion volumes in agrammatism and associated sentence deficit patterns.

Aphasia and Neurolinguistics Research Laboratory, Department of Communication Sciences and Disorders, Northwestern University

Background: Production and comprehension of syntactically complex structures are characteristic signs of agrammatism. Whereas several studies indicate that frontal brain lesions give rise to these deficits, others have found lesions extending into posterior regions (Wilson & Saygin, 2004; Caplan et al., 2007). In this study we quantified topographic and volumetric aspects of lesions in agrammatic speakers and tested for correlation between the extent of lesioned tissue in posterior regions of interest (ROIs) and subtests of the Northwestern Assessment of Verbs and Sentences (NAVS; Thompson, in preparation).
Methods: Fourteen participants with agrammatic aphasia were administered the NAVS, which includes a Verb Naming Test (VNT), Verb Comprehension Test (VCT), Argument Structure Production Test (ASPT), Sentence Production Test (SPT) and Sentence Comprehension Test (SCT). Based on T1-weighted scans, lesions were outlined and measured using MRIcro. The STG, MTG, SMG, AG, IFG and MFG were selected as regions of interest and lesioned tissue in these areas was correlated with NAVS test scores using the Pearson test.
Results: Statistical analyses showed significant negative correlations between lesion volumes in the SMG and ASPT scores ($r = -0.54$), SPT ($r = -0.60$) and SCT scores ($r = -0.62$) of the NAVS. Lesion volumes in the STG were similarly correlated with ASPT ($r = -0.54$) and the SPT scores ($r = -0.55$).
Discussion: Recruitment of the posterior perisylvian network for aspects of sentence processing, including argument structure processing has been shown in several studies (Shapiro et al. 1993; McCann and Edwards, 2002; Ben Sachar et al., 2004; Thompson et al. 2007; Bonakdarpour et al. 2007). Using lesion volumetry, we found that the superior temporal and supramarginal gyri were associated with argument structure production; when tissue in these regions is damaged, argument structure production is affected.

Kathryn Rhett Nichols and R. Casati

How do people switch frames of reference?

P56

Cog Master Program, Paris V, France

In a text-based navigation task, subjects' time delay, or 'switch cost' for a reference frame change, correlated with 3D mental rotation ability. Previous studies have examined visuospatial skills involved in human tasks, and explored the properties of two modes of navigation: route and survey perspectives, as well as transformations in different frames of reference. This study specifically asked what skill is used in switching between types of reference frame used on the same space, from a map to the immersive world. Switch costs revealed themselves with no change in terminology, moving point-of-view, or change from egocentric to allocentric coordinates, which were present in other studies. Finally, score correlation in men and lack thereof in women suggests that the gender groups used different strategies to perform equally well on the larger task.

Andrea Orthmann, R. Zeisig, and I. Fichtner

P57 Cellular uptake and delivery of a liposomal carrier across an epithelial monolayer model depends on the membrane properties

Experimental Pharmacology, Max Delbrück Center for Molecular Medicine

Background: Treatment of brain tumors and metastasis is a serious challenge of oncology because of the limited transport of drugs into the brain. Chemotherapy with systemically used hydrophilic cytostatics often failed, because of the physiological barriers, mainly the blood-brain barrier (BBB). The transport of compounds via the BBB can be improved using liposomes, because of their high lipophilic properties. An encapsulation of drugs into liposomes could improve the drug transport to the brain.
Aim: Investigation of the effect of liposomal membrane composition on the transport across a cellular barrier in vitro and in vivo.
Results: Prepared vesicles had a diameter between 100 and 200 nm and encapsulated about 40 mmol/mol total lipid. Liposomes with a positive charge and formulations which contained the helper lipid DOPE showed the most efficient uptake by Madin-Darby canine kidney (MDCK) cells in vitro with values of 190–257 nmol calcein/well. Confocal laser scanning microscopy demonstrated that liposomes were clearly endocytosed by the MDCK cells, but were also found bound to the cell membrane. Intracellular calcein was mostly accumulated into the mitochondria. In vitro transcytosis experiments, with an epithelial barrier model (MDCK cells) demonstrated the best results with liposomes containing a combination of the helper lipids DOPE and OPP with 591 pmol calcein/cm^2 found in the basal medium. Electron paramagnetic resonance measurements revealed a clear increase in transcytosis if membrane fluidity was enhanced.

In vivo studies using a human xenograft-brain cancer model (MT-3 breast cancer) present a significantly better anti-tumor effect of Mitoxantrone liposomes compared to the free drug based on the tumor volume reduction. Furthermore the liposomal treatment evidenced lower side effects (gastrointestinal complications, weight loss, dehydration, etc.).

Smadar Ovadia-Caro,[1] Y. Nir,[2] A. Soddu,[3] M. Ramot,[1] A. Vanhaudenhuyse,[3] I. Dinstein,[1] J.-F. L Tshibanda,[3] M. Boly,[3] M. Harel,[1] S. Laureys,[3] and R. Malach[1]

Decreased inter-hemispheric correlations in patients with disorders of consciousness: an fMRI study

P58

[1] Department of Neurobiology, Weizmann Institute of Science, Rehovot, Israel; [2] Department of Psychiatry, University of Wisconsin-Madison, USA; [3] Coma Science Group, Cyclotron Research Center and Neurology Department, University of Liège, Belgium

Spontaneous activity, as measured by fMRI, has several well established features which are found in healthy subjects. One of the most prominent characteristics is the inter-hemispheric correlation pattern between homologous cortical regions. These spontaneous correlation patterns replicate well known functional networks. Disorders of consciousness caused by brain injury often result in severe alterations in levels of awareness. Diagnosis of such disorders poses a great challenge in the clinic since patients are often incommunicative, and although to this day clinical examination remains the gold standard, a relatively high misdiagnosis rate is reported. Here, we studied alterations in spontaneous inter-hemispheric BOLD correlation patterns in subjects with impaired awareness due to brain injury. Identical analysis was applied to subjects with intact awareness (locked-in patients and healthy controls). Our study revealed a highly significant decrease in magnitude and spatial specificity of inter-hemispheric correlations in states of impaired awareness as compared to states of intact awareness, which were often discernable at the single-subject level. These results may serve as the basis for an objective measure, which can be developed into a complementary diagnostic tool. Such an objective tool can aid in reducing the rate of misdiagnosis, and can potentially assist in identifying patients with intact awareness (locked-in), for which the means of diagnosis are currently limited, with diagnosis on average taking 2.5 months. Our results also provide some insight into the nature of the enigmatic spontaneous activity, which has been a subject of controversy in recent years.

Supported by ISF, Bikura and Minerva grants to R.M.

Marisa Przyrembel

P59 The 2nd Person Perspective – Is it real?

Volkswagen Foundation Research Project "The brain as an organ of interrelations," Institute of Philosophy, Humboldt-Universität zu Berlin

My topic is part of the interdisciplinary project "The brain as an organ of interrelations – Interdisciplinary perspectives on the development of socially induced capacities." The project brings together psychologists, philosophers, psychiatrists, and neuroscientists from Berlin, Heidelberg, and Munich and is funded by Volkswagen Foundation. The project aims at a new approach within the present debate on consciousness of the self and other minds by relating the anthropological constituents of personal autonomy to the results of developmental and social psychology in addition to neurobiological research.

In my thesis, I will

a) define the three perspectives (first, second and third person perspective/1PP, 2PP, 3PP), show their irreducibility as well as their ontological connection and
b) illustrate the importance of the second person perspective particularly for an adequate understanding of the problem of self-consciousness.

In the latter point, I will concentrate on psychological phenomena (e.g., joint attention, middle-range model of interaction, ostracism) but also psychopathological syndromes (e.g., autism) in order to exemplify the essential role of the 2PP for a profound philosophical understanding of those phenomena, the capacity of perspective-taking or the "theory of mind."

Maria R. Restivo, E. B. Brownlie, and J. Beitchman

Speech and language impairment in women: academic pathways and early adult relationship satisfaction

P60

St. Joseph's Hospital – Mood Disorders Program, McMaster University, Hamilton, Canada

Speech and language (S/L) impairments are associated with academic difficulties and a higher likelihood of behaviour problems in childhood and adolescence. Few studies have tracked the adult psychosocial outcomes of S/L impairment, especially among women. Early exit from the education system, a lack of employment skills and attractive career options, and poor psychosocial functioning may predispose women to involvement in maladaptive intimate relationships at an early age. This study explored relationship satisfaction at age 25 in a community sample of women who had S/L impairments at age 5 and a matched control group. Relationship satisfaction with spouse or intimate partner was measured with the Dyadic Adjustment Scale; life outcome information was obtained from semi-structured interviews. Women with S/L impairment were less likely to participate in post-secondary education than controls and had a lower annual income. S/L impairment was not directly associated with relationship satisfaction. However, an interaction of education and S/L impairment indicated that a higher level of education was associated with increased relationship satisfaction for control women, but not for S/L impaired women. Possible moderating pathways that may lead to the differential relationship outcomes for the two groups of women are discussed.

Rosanne L. Rademaker, J. Pearson, and F. Tong

P61 Picture perfect: The training of visual imagery

Vanderbilt University, Nashville, USA

Can visual imagery improve by means of training? We tried answering this question by having participants imagine colored Gabor gratings for 140 trials a day, over the course of five consecutive days, and two-to-three weeks after the end of training. On each trial, after eight seconds of imagery, participants were confronted with a binocular rivalry display consisting of two gratings presented to the two eyes. The influence of imagery on dominance facilitation during rivalry was taken as an outcome measure. Participants were trained on one set of oriented gratings to see if their performance would change over time. We found above chance bias of imagery, but no main effect of training over time. Subjective measures were also collected on each trial to see how vivid imagery was and how much effort participants exerted. When the data were split according to subjective vividness, imagery facilitation was stronger for high vividness trials than it was on low vividness trials. Moreover, training increased dominance facilitation due to imagery over the course of time for trials on which vividness of the imagined stimuli was high. We furthermore discovered that the correlation between subjective vividness and effort ratings tended to increase over the course of training.

Can visual imagery improve by means of training? We tried answering this question by having participants imagine colored Gabor gratings for 140 trials a day, over the course of five consecutive days, and two-to-three weeks after the end of training. On each trial, after eight seconds of imagery, participants were confronted with a binocular rivalry display consisting of two gratings presented to the two eyes. The influence of imagery on dominance facilitation during rivalry was taken as an outcome measure. Participants were trained on one set of oriented gratings to see if their performance would change over time. We found above chance bias of imagery, but no main effect of training over time. Subjective measures were also collected on each trial to see how vivid imagery was and how much effort participants exerted. When the data were split according to subjective vividness, imagery facilitation was stronger for high vividness trials than it was on low vividness trials. Moreover, training increased dominance facilitation due to imagery over the course of time for trials on which vividness of the imagined stimuli was high. We furthermore discovered that the correlation between subjective vividness and effort ratings tended to increase over the course of training.

Anja Schreiter,[1] B. P. Roques,[2] M. C. Fournié-Zaluski,[2] C. Stein,[1] and H. Machelska[1]

Blockade of peptidases in immune cells and peripheral nerves to enhance opioid-mediated inhibition of inflammatory pain

P62

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Background and aims. Degradation of opioid peptides by aminopeptidase N (APN) and neutral endopeptidase (NEP) has been extensively examined in the CNS. Our goal was to investigate the prevention of opioid peptide catabolism with inhibitors of NEP (thiorphan) and of APN (bestatin) as well as a novel dual inhibitor P8B to enhance analgesic effects of opioids in inflamed painful tissue.
Methods. Experiments were performed at 4 days after injection of complete Freund's adjuvant into one hind paw in rats. Enzyme expression was analyzed in immune cells and sciatic nerves isolated from inflamed paws, using flow cytometry and immunoblotting. Enzymatic activity of APN and NEP was measured spectrometricaly. Opioid peptide amounts were assessed with radioimmunoassay.
Results. APN and NEP were expressed in peripheral nerves and in macrophages and granulocytes, but not in T lymphocytes, in inflamed painful tissue. In in vitro leukocyte or sciatic nerve suspensions APN and NEP cleaved their specific exogenously added substrates (Ala-β-naphthylamin and Suc-Ala-Ala-Phe-p-nitroanilin, respectively) that could be blocked with single and dual inhibitors. Importantly, degradation of Leu-enkephalin, but not of β endorphin, was prevented by a combination of thiorphan and bestatin or by P8B.
Conclusions. We show for the first time that degradation of opioid peptides can be prevented by blockade of APN and NEP expressed in immune cells and peripheral nerves in painful inflamed tissue. Enkephalins appear as preferred substrates for NEP and APN. Inhibiting the enzymatic degradation of opioids offers a promising strategy for the pain control without adverse centrally-mediated side effects.

Patricia Seja, G. Spitzmaul, C. Pfeffer, and T. J. Jentsch

P63 The physiological role of KCC2 in the cerebellum

Physiology and Pathology of Ion Transport, Max Delbrück Center for Molecular Medicine and Leibniz Institute for Molecular Pharmacology

Cation chloride cotransporters mediate a coupled electroneutral movement of Cl^-, K^+ and Na^+ across plasmamembranes in many cells. The neuron-specific KCl cotransporter KCC2 is thought to lower the intracellular Cl^- concentration below its electrochemical equilibrium potential by using the outwards directed gradient of K^+ as a driving force. This low intracellular Cl^- concentration is required for the fast inhibitory action of GABA which is mediated by the GABAA receptor, a ligand-gated anion channel.

The activation of GABAA receptors drives the membrane potential of a cell towards EGABA, the reversal potential of GABAergic currents. In immature neurons, GABA is excitatory, as EGABA is above the resting membrane potential. The expression of KCC2 correlates with the drop of EGABA below the resting membrane potential, and thereby the switch from excitatory to inhibitory GABA signaling.

The KCl cotransporter KCC3 is expressed more broadly and involved in cell volume regulation. Nevertheless, while KCC2 may be the key regulator of neuronal $[Cl^-]_i$, a similar role was proposed for KCC3. We investigate the physiological role of KCC2 and KCC3 in the murine cerebellum at cellular level via the patch clamp technique in acute slices. We showed that knocking out KCC2 in cerebellar Purkinje cells results in a shift of EGABA, which could be correlated with motor learning deficits.

Joulia Smortchkova

A step toward a naturalization of monothematic delusional beliefs P64

Institut Jean Nicod, Paris, France

Monothematic delusional beliefs are a challenge both for the scientist and the philosopher. How could it be that an overall rational person, with no impairment of memory and of logical reasoning, can hold a circumscriptive belief about a fact *x*, which is false? In this work, did under the supervision of Prof. Pacherie at Institut Jean Nicod, different possibilities of a naturalistic account for delusional beliefs were explored. Starting from dual approaches, passing through purely neuroscientific accounts, we advanced a complex approach in order to account for their multiple aspects. We argued for a multi-level and functional approach, considering monothematic delusional beliefs as complex cognitive natural kinds. This new framework can constitute a step for further research, without reducing the problem to one of its aspects.

Marina Trakas

P65 Episodic memory in human and non-human animals

École des Hautes Études en Sciences Sociales, Institut Jean Nicod, Paris, France

Episodic memory is the kind of declarative memory of events and episodes experienced in the past. The author of this concept, Endel Tulving, thinks that episodic memory is unique to humans. However, some researchers have experimented with non-human animals to prove the opposite thesis. In this work we will review this discussion, which will lead us to analyze the definitions and the different reformulations that the episodic memory concept has suffered over time.

Corinde E. Wiers and M. R. Yeomans

Human individual differences in umami taste; synergism with IMP and odor and its relation to taste bud anatomy

P66

Department of Psychology, University of Sussex, Brighton, England

The protein taste named 'umami' generated by the presence of monosodium glutamate (MSG) on the tongue has been identified as distinct from the taste qualities bitter, sweet, sour and salt. The hedonic and sensory character of MSG is not yet fully understood, and humans have been shown to vary in their recognition of the taste. On its own, umami is perceived as unpleasant, whereas its combination with a savoury odour produces a highly pleasurable flavour experience. Moreover, the combination of MSG with a ribonucleotide, ionosine monophosphate (IMP), enhances the perception of umami. Over the last decade, various receptors involved in umami taste have been identified: the TAS1R1-TAS1R3 heterodimer and two truncated metabotropic glutamate receptors, mGluR1 and mGluR3. Recently, polymorphisms of these receptors in humans have been found that partly explain individual differences in sensory experiences of umami. Since the amount of fungiform papillae on the surface of the human tongue is strongly correlated with the perception of bitter compound 6-n-propylthiouracil (PROP), this study examines the hypothesis that individual differences in umami taste perception and synergism with IMP can be explained by variation in fungiform papillae density (FPD). 42 healthy subjects taste 1.0 mM MSG, 29.0 mM NaCl and H_2O stimuli, in the presence and absence of vegetable odour and 1.0 mM IMP. The amount of fungiform papillae is measured along with bitter taster status, based on sensitivity of 3.2 mM PROP and 1.0 M NaCl. Although FPD was a significant predictor of bitter intensity, it was not for umami intensity, nor for IMP synergism. Future studies should address the combination of polymorphisms in the TAS1R1-TAS1R3 genes and FPD, in exploring the genotypic base for umami sensitivity.

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"

GRK 1258: The Impact of Inflammation on Nervous
System Function

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"

Ph.D. Program Coordination Prof. Dr. U. Dirnagl, Prof. Dr. U. Heinemann, Prof. Dr. R. Nitsch, Dr. U. Lindauer and M. Munz

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.

A two-year M.Sc. program prepares students for continued doctoral education in neuroscience. During the three-year Ph.D. 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, Ph.D. students organize the international Ph.D. symposium "Berlin Brain Days." The Ph.D. degree is awarded based on three publications or a dissertation.

NeuroCure – Scientific Coordinator: Prof. Dr. Dietmar Schmitz
In 2008, the Ph.D. program became the "educational arm" of the Cluster of Excellence "NeuroCure." This interdisciplinary consortium unites 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 a combined 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 zu Berlin and Technische Universität Berlin, 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 at the moment funded by the Federal Ministry of Education and Research (BMBF) will from 2010 on continue as the Graduiertenkolleg "Sensory Computation in Neural Systems" funded by the DFG. 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 Ph.D. students are required to attend courses on advanced "hard skill" topics, such as methods of machine learning and artificial intelligence in addition to computational and experimental neuroscience, as well as "soft skills."

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. Arno Villringer and Prof. Dr. Michael Pauen

The Berlin School of Mind and Brain is an international research school. Founded in 2006 as part of Germany's Excellence Initiative, it offers a three-year interdisciplinary doctoral 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's faculty comprises 60 distinguished researchers, including four Max Planck directors. Hosted by Humboldt-Universität zu Berlin, the School's research program includes scientists from Freie Universität, Charité, 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 international lecture series, journal and methods clubs, poster presentations, conferences and workshops. They are obliged to take a number of scientific soft-skill courses such as presentation skills, grant-application writing, scientific writing, and are offered dissertation coaching, mentoring, and career advice.

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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 of the 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 Ph.D.-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 faculty comprises researchers from the Max Delbrück Center for Molecular Medicine Berlin-Buch, Freie Universität Berlin, and Charité – Universitätsmedizin Berlin.

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NEURO
INFLAMMATION
research training school 1258

GRK 1258: The Impact of Inflammation on Nervous System Function

Spokespersons Prof. Dr. Helmut Kettenmann and Prof. Dr. Frauke Zipp

The Research Training Group 1258 "The Impact of Inflammation on Nervous System Function" has the goal to train Ph.D. students in the neurosciences with the special topic neuroinflammation. There is increasing evidence that immunological processes are involved not only in the classical inflammatory disorders of the nervous system but also in primarily non-inflammatory injuries, such as Alzheimer disease and stroke. Although the initiating events differ considerably, we hypothesize common pathways in the crosstalk between immune and nervous system in the course of these diseases. The focus of this graduate program is on the interaction of proinflammatory and regulatory immune cells with cells of the cells of the central and peripheral nervous system, such as astrocytes, microglia and neurons. The microglial cell has many common properties with macrophages and plays a central role as an interphase between immune cells and neurons. The faculty of this graduate program studies this crosstalk by combining modern methods of molecular and cellular biology with imaging techniques such as two photon microscopy or magnetic resonance imaging.

The program started on April 1, 2006 and has on average 5 students with a medical and 10 students with a science background. The graduate program is integrated into the Humboldt-Universität's International Masters-M.D./Ph.D. Program "Medical Neurosciences." By enrolling into this program the students will have the opportunity to participate in lectures and courses on the M.D./Ph.D. program. The students are recruited both from Germany and internationally. The Graduate School provides an excellent platform to acquire training on the theoretical level as well as on technical skills.

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International Graduate School "Languages of Emotion"

Cluster Coordinator Prof. Dr. Winfried Menninghaus

The international graduate school "Languages of Emotion" offers a 3-year Ph.D. program for graduate students who have already earned an M.A. degree or the equivalent. A "fast track" admission will be offered to outstanding students who have only completed the first year of their postgraduate M.A. and, in exceptional cases, to excellent B.A. graduates.

This doctoral program is part of the interdisciplinary cluster "Languages of Emotion" which focuses on the interdependencies between language and affect. The cluster's four research areas address the following topics: (1) the relations between affective phenomena and various representational media (language, sound, image); (2) the artistic practices and poetics of (re)presenting/shaping emotions; (3) correlations between emotional and linguistic competencies (and their disorders); and (4) modes of emotion modeling at the level of cultural codes and patterns of social behavior.

The cluster brings together academic expertise from more than 20 disciplines with their own traditions of addressing emotion, such as Anthropology, Near Eastern Studies, Biology, Film Studies, Japanese Studies, History of Art, Literary History and Criticism, Musicology, Philosophy, Political Science, (Neuro-)Psychology, Psychiatry, Religious Studies, Sociology, Linguistics, Theater and Dance Studies.

During the first year of the doctoral program, students will attend courses that concentrate on selected theoretical models and methodologies in the respective disciplines. In their second year students will attend one interdisciplinary seminar focusing exclusively on the field of research conducted by the cluster itself. Soft-skill courses will be offered in cooperation with the "Dahlem Research School." During the second year, students will be offered the opportunity to continue their studies abroad for about three months. We provide ten stipends per year (approx. €1,500 per month). Up to five additional Ph.D. students with funding from sources other than the cluster will be admitted to the program each year.

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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 10.12.2009 bis 11.12.2009

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

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

gültig vom 10.12.2009 bis 11.12.2009

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

ap = barrierefrei
bf = barrierefrei

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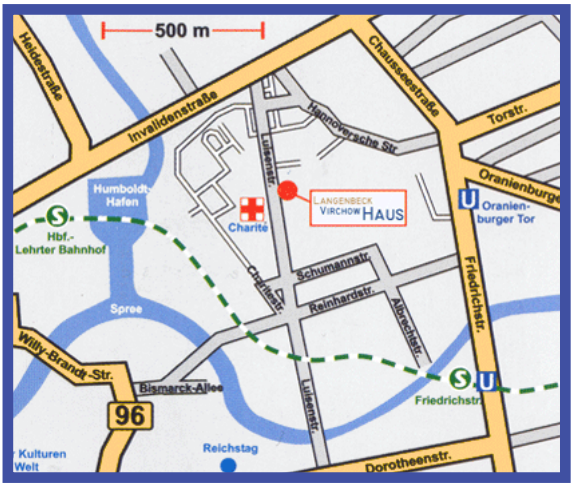

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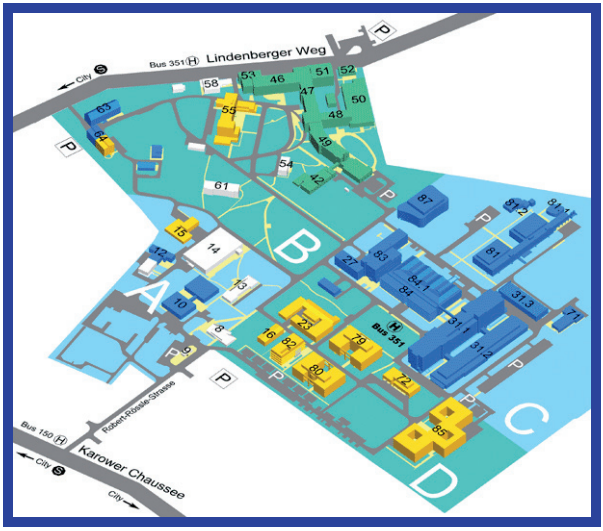

Max Delbrück Center for Molecular Medicine, Berlin-Buch
Conference Center MDC.C (labeled 83 on the map), Lecture hall “Axon”
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The **Berlin Brain Days** 2009 are jointly organized by seven Berlin-based neuroscience Ph.D. programs:

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

Graduate School
"The Impact of Inflammation on Nervous System Function"
DFG-Graduiertenkolleg 1258

Berlin, Charité
International Graduate Program Medical Neurosciences

LANGUAGES OF EMOTION

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

BERLIN SCHOOL OF MIND AND BRAIN

HUMBOLDT-UNIVERSITÄT ZU BERLIN

www.neuroscience-berlin.de/bbd/