June 5 - 7, 2008

BNF2008

Berlin Neuroscience Forum 2008

Program
Abstracts

Liebenwalde

The Berlin Neuroscience Forum 2008 is sponsored by

Brainclincs Diagnostics
PAA Laboratories GmbH
Millipore Bioscience

The Berlin Neuroscience Forum 2008 is the final colloquium of the SFB 507 "The Role of Non-Neuronal Cells in CNS disease"

This meeting is a joint activity of

Berlin Neuroimaging Center

Berlin School of Mind and Brain

Bernstein Center for Computational Neuroscience

Clinical Research Unit „Molecular Mechanisms of Opioid Analgesia in Inflammatory Pain"

Doctoral Research Program „Computational Neuroscience"

GRK „Cellular Mechanisms of Learning and Memory - Consolidation in the Hippocampal Formation"

GRK „Functional Insect Science"

GRK „Neuropsychiatry und Psychology of Aging"

GRK „The Impact of Inflammation on Nervous System Function"

International Graduate Program „Medical Neuroscience"

NeuroCure: Towards a Better Outcome of Neurological Disorders

Research Unit „Conflicts as Signals in Cognitive Systems"

SFB „Theoretical Biology"

SFB „Developmental Disturbances in the Nervous System"

SFB "The Role of Non-Neuronal Cells in CNS disease"

SFB/TR "Mesial Temporal Lobe Epilepsies"

SFB/TR "The Brain as a Target of Inflammatory Processes"

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Program Committee

Ingolf Blasig
Gabriel Curio
Ulrich Dirnagl
Karl Einhäupl
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Isabella Heuser
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Bertram Wiedenmann
Laurenz Wiskott
Frauke Zipp

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Homepage

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General Information

Registration	Thursday, June 5, 2008	**12.00 - 15.00**
Office Hours	Thursday, June 5, 2008 Friday, June 6, 2008 Saturday, June 7, 2008	**12.00 - 19.30** **8.30 - 19.00** **8.30 - 13.00**
Office Phone	0160 90218506	
Poster Boards	Height : 120 cm Width: 100 cm	
Poster Sessions	**Poster Session I** Poster No. 1- 59 Thursday, June 5, 2008 Friday, June 6, 2008 !!! Posters must be removed immediately after the poster session on Friday !!!	 **15.35 - 17.00** **10.00 - 11.00**
	Poster Session II Poster No. 60 - 110 Friday, June 6, 2008 Saturday, June 7, 2008	 **16.00 – 17.30** **10.00 - 11.00**
Duration of Oral Presentations	**Invited Speakers**	45 min (talk) 15 min (disc.)
	Welcome to Berlin Presentations	20 min (talk) 10 min (disc.)
	Young Investigator Presentations	10 min (talk) 5 min (disc.)

Scientific Program

Thursday, June 5, 2008

12.00 – 14.30 Arrival and Registration

14.30 – 14.35 Welcome: **Helmut Kettenmann**

14.35 - 15.35 **Lecture I**
Chair: Isabella Heuser
Carl Deisseroth
Department of Bioengineering, Department of Psychiatry, Stanford, USA
Optogenetics: development and neuropsychiatry application

15.35 – 17.00 **Poster Session I and Coffee Break**

17.00 – 18.00 **Welcome to Berlin Session**
Chair: Robert Nitsch

Peter Vajkoczy
Charité - Universitätsmedizin Berlin, CVK, Klinik für Neurochirurgie
Angiogenesis in malignant brain tumors

Felix Wichmann
Technische Universität Berlin, FG Modellierung Kognitiver Prozesse
Modelling of cognitive processes

18:00 – 19:00 **Lecture II**
Chair: Bernhard Ronacher
Uwe Homberg
Fachbereich Biologie, Tierphysiologie, Philipps-Universität Marburg
Neural mechanisms of sky compass orientation in an insect

19.30 **Dinner and Informal Get-together**

Friday, June 6, 2008

8.00 – 9.00 **Breakfast**

9.00 – 10.00 **Lecture III**
Chair: Arno Villringer
Patrick Haggard
University College London, Institute of Cognitive Neuroscience & Department of Psychology, London, UK
Touch, vision and mental body representation

10.00 – 11.00 **Poster Session I and Coffee Break**

11.00 – 12.00 **Young Investigator Presentations Session I**
Chair: Gary Lewin

Jing Hu
Neuroscience, MDC
A tether required for touch

Ulrich Schweizer
Neurobiology of Selenium, Charité
Genetic dissection of selenprotein functions in neuronal function and survival

Christel Bonnas
Experimental Neurology, Charité
Neuroprotection by novel endogenous non-hematopoietic erythropoietin derivates

Seija Lehnardt
Cecilie-Vogt-Clinic for Neurology, Charité
A vicious cycle involving release of HSP60 from injured cells and activation of TLR4 mediates neurodegeneration in the CNS

12.00 – 13.00 **Lunch**

13.00 – 15.00 **Outdoor activities**

15.00 – 16.00 **Lecture IV**
Chair: Uwe Heinemann
Thomas Misgeld
Institut für Neurowissenschaften, Technische Universität München
In vivo imaging of axon remodeling

16.00 – 17.30 **Poster Session II and Coffee Break**

17.30 – 18.30 **Lecture V**
Chair: Ulrich Dirnagl
Brian MacVicar
Department of Psychiatry, Brain Research Center, UBC Hospital, Vancouver, Canada
Astrocyte regulation of the cerebrovasculature

18.30 – 19.30 **Dinner**

20.30 **Farewell Party SFB 507 and Disco Night**

Saturday, June 7, 2008

8.00 – 9.00 **Breakfast**

9.00 – 10.00 **Young Investigator Presentations Session II**
Chair: Dietmar Schmitz

Hannes Schmidt
Developmental Neurobiology, MDC
A cyclic GMP signaling pathway essential for sensory axon bifurcation

Oliver Kann
Neurophysiology, Charité
Mitochondria and neuronal activity: insights from the healthy and the epileptic hippocampus

Ana-Luisa Pina
Center for Regenerative Therapies, Charité
Pigment epithelium derived factor during postnatal development, ageing and disease of the Nervous System

Lars Bertram
Genetics and Aging Research Unit, MIND
Implications from systematic meta-analyses of genetic association studies of Alzheimer's disease and Parkinson's disease

10.00 – 11.00 **Poster Session II and Coffee Break**

11.00 – 11.45 **Young Investigator Presentations Session III**
Chair: Christoph Stein (Berlin)

Hagen Wende
Mouse Genetics, MDC
c-Maf is an important regulator of myelination in the peripheral nervous system

Nikolas Offenhauser
Experimental Neurology, Charité
Alterarions in neurometabolic-neurovascular coupling by cortical spreading depression in rat somatosensory cortex

Sebastian Ivens
Neurophysiology, Charité
Differential mechanisms underlying altered neuronal excitability following blood-brain barrier disruption

11.45 - 12.45 **Lecture VI**
Chair: Frauke Zipp
Britta Engelhardt
Theodor-Kocher-Institut, Universität Bern, Switzerland
Molecular mechanisms involved in tissue specific leukocyte diapedesis across the endothelium

12.45 - 13.00 **Poster Prize Awarding**

13.00 **Lunch and Departure**

Poster Presentations - Session I

Thursday, June 5, 15.35 - 17.00
Friday, June 6, 10.00 - 11.00

1. DETECTION OF SIGNALING PATHWAY ACTIVATION IN RAT DRG-NEURONS BY AUTOMATED RELATIVE IMMUNOFLUORESCENCE
Andres, C.; Hucho, T.
Max Planck Institute for Molecular Genetics, Department Ropers, Berlin

2. DEVELOPMENT OF GENETIC TOOLS FOR SELECTIVE AND REVERSIBLE SILENCING OF ION CHANNELS USING NATURAL TOXINS
Auer, S.; Jüttner, R.; Ibanez-Tallon, I.
Max-Delbrück Center for Molecular Medicine, Department of Neurobiology, Berlin

3. A MODEL OF NEURONAL COLOR CODING AND COLOR SENSATIONS IN MAN
Backhaus, W.G.K.
Technische Universität Berlin, Theoretische und Experimentelle Biologie, Neurowissenschaften, FR 2-1 R 2073, Berlin

4. SODIUM CURRENTS IN IMMORTALIZED AND DEVELOPING STRIATAL PROGENITOR CELLS
Battefeld, A.; Wasner, U.; Geist, B.; Nitsch, R.; Strauss, U.
Charité Universitätsmedizin Berlin, Centre for Anatomy, Institute for Cell and Neurobiology, Berlin

5. ALCOHOL MEDIATES ASSOCIATION BETWEEN STRIATAL REWARD PROCESSING AND IMPULSIVENESS
Beck, A.; Deserno, L.; Kahnt, T.; Wrase, J.; Heinz, A.
Charité - Universitätsmedizin Berlin, CCM, Department of Psychiatry and Psychotherapy, Berlin

6. ROLE OF EXTRACELLULAR SIGNAL-RELATED KINASE 1 IN THE REGULATION OF NEUROINFLAMMATION
Bendix, I.; Pfueller, C.F.; Leuenberger, T.; Siffrin, V.; Schulze-Topphoff, U.; Zipp, F.; Waiczies, S.
Charite University Medicine Berlin, Cecile Vogt Clinic for Neurology at the HKBB, Berlin

7. CLC-2 CL- CURRENTS IN OLIGODENDROCYTES FROM ACUTE SLICES IN THE MOUSE CORPUS CALLOSUM
Benedetti, B.; Haas, B.; Jentsch, T. J., Kettenmann, H.
MDC, Cellular Neuroscience, Berlin

8. SYNERGISTIC EFFECTS OF IL-4 AND IL-10 ON AXONAL OUTGROWTH AND REINNERVATION
Boato, F.; Hechler, D.; Rosenberger, K.; Nitsch, R.; Hendrix, S.
Charité – Universitätsmedizin, Institute for Cell Biology and Neurobiology, Center for Anatomy, Berlin

9. MIGRATION OF GENE-MODIFIED BONE MARROW-DERIVED CELLS INTO MOUSE RETINAS
Boettcher, C.; Beck, S.; Bauer, R.; Seeliger, M.W.; Priller, J.
Charité Campus Mitte, Laboratory of Molecular Psychiatry, Berlin

10. MECHANISMS AND FUNCTIONAL ROLE OF IMMUNE RESPONSE FOLLOWING AXONAL LESION
Brandt, C.; Meisel, C.; Richter, D.; Ellinghaus, A.; Bechmann, I.; Nitsch, R.
Institute of Cellbiology and Neurobiology, Center for Anatomy, Berlin

11. B56BETA INTERACTS WITH CALEB/NGC AND INHIBITS CALEB/NGC-MEDIATED DENDRITIC BRANCHING
Brandt, N.; Nitsch, R.; Schumacher, S.
Institute of Cell Biology and Neurobiology, Charité-Universitätsmedizin Berlin, Center for Anatomy, Berlin

12. LATERAL LINE RESPONSES INTEGRATE THE WAVE CURVATURE
Branoner, F.; Ziehm, U.; Zhivkov, Z.; Schuldt, C.; Behrend, O.
Humboldt Universität Berlin, Institute of Biology, Aquatic Bioacoustics Laboratory, Berlin

13. DYSFERLIN DEFICIENT MUSCULAR DYSTROPHY FEATURES AMYLOIDOSIS
Carl, M.; Zabojszcza, J.; Bushby, K.; Moore, S.A.; Röcken, C.; Spuler, S.
Experimental and Clinical Research Center (ECRC), Charité Universitary Medical S, Muscle Research Unit, Berlin

14. ROLE OF G-ALPHAI2 ON ZO-1 UNDER EPINEPHRINE STIMULATION
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Leibniz-Institut für Molekulare Pharmakologie, Molecular Cell Physiology, Berlin

15. PERSONALITY TRAITS AND STRUCTURAL BRAIN ALTERATIONS IN HEALTHY SUBJECTS: A MORPHOMETRIC ANALYSIS OF MRI-DATA
Charlet, K.; Gudlowski, Y.; Kaufmann, C.; Schubert, F.; Heinz, A.; Gallinat, J.
Charité - University Medicine Berlin, Department of Psychiatry and Psychotherapy Campus Mitte, Berlin

16. AMEBOID MICROGLIA IN DEVELOPING BRAIN INDIRECTLY RESPOND TO GABA- AND GLUTAMATERGIC ACTIVITIES BY SENSING THE RESULTING INCREASE IN EXTRACELLULAR POTASSIUM
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MDC, Cellular Neuroscience, Berlin

17. ROLE OF EXTRACELLULAR MATRX IN SENSORY MECHANOTRANSDUCTION
Chiang, L.Y.; Hu, J.; Erdmann, B.; Koch, M.; Lewin, G.R.
Max-Delbrück Centrum, Neuroscience, Berlin

18. MODULATION OF NEURONAL MEMBRANE PROPERTIES BY THE COXSACKIEVIRUS-ADENOVIRUS RECEPTOR
Cholewa, J.; Jüttner, R.; Rathjen, F.G.
Max Delbrück Center for Molecular Medicine (MDC) Berlin-Buch, Developmental Neurobiology, Berlin

19. PRG-5 IN CULTURED NEURONS INDUCTS DENDRITIC-SPINES FORMATION
Coiro, P.; Velmans, T.; Bräuer, A.U.
Charite, Institut für Zell- und Neurobiologie, Berlin

20. DEVELOPMENTALLY REGULATED EXPRESSION, LOCALIZATION AND FUNCTIONAL REGULATION OF CALEB, AN EGF-LIKE PROTEIN
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Max-Delbrück-Centrum für Molekulare Medizin, Neurobiology, Berlin

21. COMPLEMENTARY CONTRIBUTIONS OF PREFRONTAL NEURON CLASSES IN ABSTRACT NUMERICAL CATEGORIZATION
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Hertie Institute for Clinical Brain Research, Cognitive Neurology, Tübingen

22. ALPHA-1A ADRENERGIC RECEPTORS REGULATE NEUROGENESIS AND COGNITIVE FUNCTION
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Univ. of North Dakota School of Medicine Health Sciences, Pharmacology, Physiology Therapeutics, Grand Forks, North Dakota

23. 'NORMAL' AND 'INVERSE' NEUROVASCULAR COUPLING AND SUPPRESSION OF LOW-FREQUENCY VASCULAR FLUCTUATIONS DURING CORTICAL SPREADING DEPOLARISATION IN THE HUMAN BRAIN
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Charité University Medicine Berlin, Neurology, Berlin

24. GLYCINERGIC TONIC INHIBITION OF HIPPOCAMPAL NEURONS WITH DEPOLARISING GABAERGIC TRANSMISSION ELICITS HISTOPATHOLOGICAL SIGNS OF TEMPORAL LOBE EPILEPSY
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MDC, Neuroscience, Berlin

25. COMPLEMENT C1Q IS A PROINFLAMMATORY STIMULUS, AND MANNOSE-BINDING LECTIN IS AN ANTI-INFLAMMATORY STIMULUS, FOR MICROGLIAL ACTIVATION
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MDC, Cellular Neuroscience, Berlin

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Freie Universität Berlin, Neurobiologie, Berlin

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Charité - Universitätsmedizin Berlin, Department of Experimental Neurology, Berlin

28. HETEROSYNAPTIC PLASTICITY AT THE HIPPOCAMPAL OUTPUT
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Charité Universitaetsmedizin, Institute for Neurophysiology, Berlin

29. INVESTIGATION OF SIGNALLING PATHWAYS NECESSARY FOR CALEB/NGC- DRIVEN DENDRITIC SPINE COMPLEXITY
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Institute of Cell Biology and Neurobiology, Charité-Universitätsmedizin Berlin; Centre for Anatomy, Berlin

30. NEUROVASCULAR COUPLING AND CEREBRAL METABOLIC RATE OF OXYGEN: EFFECTS OF BRAIN HYPOTHERMIA
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Charite Universitätsmedizin Berlin, Department of Experimental Neurology, Berlin

31. ROLE OF THE TSH1 GENE IN OLFACTORY BULB - DEVELOPMENT
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Max-Delbrueck-Center for Molecular Medicine, Department of Neurosciences, Berlin

32. EXPRESSION ANALYSIS OF THE PLASTICITY RELATED GENE-1
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Charité-Universitätsmedizin Berlin, Center für Anatomie, Institut für Zell- und Neurobiologie, Berlin

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Charite-Klinik f. Psychiatrie u. Psychotherapie, Charite Campus Mitte, Molekulare Psychiatrie, Berlin

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Berlin School of Mind and Brain, Berlin

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Charité-Universitätsmedizin Berlin, Zentrum für Anatomie, Berlin

36. TRPV1, A SYNAPTIC PROTEIN
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Max Planck Institute for Molecular Genetics, Signal Transduction in Pain and Mental Retardation, Berlin

37. EFFECTS OF SALICYLATE APPLICATION ON THE SPONTANEOUS ACTIVITY IN BRAIN SLICES OF THE MOUSE COCHLEAR NUCLEUS, MEDIAL GENICULATE BODY AND PRIMARY AUDITORY CORTEX
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Humboldt-University Berlin, Department of Biology, Neurootological Team, Berlin

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Humboldt-University of Berlin, Institute of Biology, Berlin

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Institute for Neurophysiology, Charite Universitätsmedizin Berlin

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Charité - University Medicine Berlin, Cecilie Vogt Clinic of Neurology, Berlin

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Institute of Pharmacology and Toxicology, Freie Universität Berlin, Dept. of Veterinary Medicine, Berlin

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Charité, Institut für Neurophysiologie, Berlin

43. MOLECULAR INTERACTIONS BETWEEN STOMATIN-LIKE PROTEINS AND ACID-SENSING ION CHANNELS
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Charité CBF, Klinik fuer Anaesthesiologie, Berlin

44. CALEB, AN ACTIVITY-REGULATED PROTEIN, IS INVOLVED IN THE ESTABISHMENT OF SYNAPTIC CONNECTIONS IN THE CEREBELLUM
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Developmental Neurobiology, MDC, Berlin

45. EARLY MATURATION OF GABAERGIC SYNAPSES IN MOUSE RETINAL GANGLION CELLS
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46. LYSOPHOSPHATIDIC ACID IN SYNAPSOGENESIS
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Charité, Centrum for Anatomy, Cell- and Neurobiology, Berlin

47. DRUG TRANSPORTERS IN HUMAN EPILEPTIC BRAIN – FUNCTIONAL STUDIES
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Charité, Institut für Neurophysiologie, Berlin

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Institut für Neurophysiolgie, Charité-Universität-Medizin Berlin, Developmental Physiology, Berlin

49. ACTIVITY OF THE GABA TRANSPORTER 1 REGULATES GABAERGIC SYNAPTIC TRANSMISSION IN STRIATAL PROJECTION NEURONS
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Inst. for Neurophysiology - Charité, Developmental Physiology, Berlin

50. METABOLIC CONSEQUENCES OF STORE OPERATED CAPACITATIVE CA2+ ENTRY
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Charite-Universitaetsmedizin, Berlin, Inst. for Neurophysiology, Berlin

51. ESTROGEN INDUCES TRPV1-DEPENDENT CYTOSKELETAL REARRANGEMENT
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MPI for Molecular Genetics, Berlin

52. SEQUENTIAL MATURATION OF SENSORY NEURON MECHANOTRANSDUCTION DURING EMBRYONIC DEVELOPMENT
Lechner, St.G.; Wang, R.; Frenzel, H.; Lewin, G.R.
Max Delbrück Centrum für Molekulare Medizin (MDC) Berlin-Buch, Neurowisssenschaften, Berlin

53. DOES AGING INFLUENCE PHYSIOLOGICAL NEUROVASCULAR COUPLING? A COMBINED DC-MAGNETOENCEPHALOGRAPHIC AND TIME-RESOLVED NEAR-INFRARED SPECTROSCOPIC STUDY
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Charité, Campus Benjamin Franklin, Department of Neurology, Berlin

54. MOLECULAR MECHANISMS UNDERLYING AMYLOID BETA MODULATING EFFECTS OF FENOFIBRATE AND CELEBREX
Lill, C.M.; Thomas, A.V.; Herl, L.; Deng, A.; Hyman, B.T.; Berezovska, O.
Cecilie Vogt Clinic for Neurology, Charité Berlin, Neurology, Berlin

55. OLIGODENDROCYTIC COUPLING IN THE CNS WHITE MATTER RELATED TO CX47 EXPRESSION
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MDC, Cellular Neuroscience, Berlin

56. DURATION OF CORTICAL SPREADING ISCHEMIA DEPENDS ON INTRACELLULAR CA2+-STORES.
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Charité -Universitätsmedizin Berlin, Experimental Neurology, Berlin

57. CHARACTERIZATION OF THE PERIPHERAL OSMORECEPTOR
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MDC, Neuroscience, Berlin

58. THE POTASSIUM THRESHOLD FOR CORTICAL SPREADING DEPRESSION IS INFLUENCED BY AGE AND EPILEPTIC CHANGES IN RAT AND HUMAN NEOCORTEX
Maslarova, A.; Alam, M.; Dreier, J.P.
Charité, Berlin, Experimental Neurology, Berlin

59. GABAB RECEPTOR MEDIATED INHIBITION IN MESIAL TEMPORAL LOBE EPILEPSY
Maziashvili, N.; Dugladze, T.; Heinemann, U.; Gloveli, T.
Institute for Neurophysiology, Charité-Universitätsmedizin, Berlin

List of Poster Presentations – Session II

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Saturday, June 7, 10.00 - 11.00

60. HEXOKINASE II - A GLUCOSE DEPENDENT MEDIATOR OF SURVIVAL
Mergenthaler, P.; Freyer, D.; Neeb, L.; Megow, D., Harms, C.; Priller, J.; Dirnagl, U.; Meisel, A.
Charité Universitätsmedizin Berlin, Experimentelle Neurologie, Berlin

61. ROLE OF DIFFERENT CTL-EFFECTOR MOLECULES IN DAMAGING THE NEURO-AXONAL UNIT IN VIVO
Merkler, D.; Bergthaler, A.; Schedensack, M.; Horvath, E.; Kerschensteiner, M.; Misgeld, T.; Brück, W.; Pinschewer, D.
Georg-August-University, Neuropathology, Göttingen

62. MODULATION OF THERMAL NOCICEPTION BY NGF AND SCF/C-KIT SIGNALING
Milenkovic, N.; Frahm, C.; Griffel, C.; Erdmann, B.; Birchmeier, C.; Garratt, A.; Lewin, G.R.
Max-Delbrück Centrum für molekulare Medizin, Berlin

63. ANALYSIS OF OPIOID RECEPTOR/K+ CHANNEL COUPLING IN SENSORY NEURONS
Nockemann, D.; Stein, C.; Heppenstall, P.A.
Klinik für Anästhesiologie und operative Intensivmedizin, Charité, Berlin

64. DOES ENOTHELIN-1 INDUCE CORTICAL SPREADING DEPOLARIZATION (CSD) VIA A DIRECT EFFECT ON THE VASCULATURE?
Oliveira-Ferreira, A.I.; Alam, M.; Major, S.; Dreier, J.P.
Charité University Medicine, Experimental Neurology, Berlin

65. RHOG IS A TARGET FOR MI-RNA DEPENDENT REGULATION OF EXPRESSION AND HAS AN IMPACT ON AXONAL BRANCHING
Otto, W.; Baumgart, J.; Dulinski, M.; Wulczyn, F.G.; Nitsch, R.; Schumacher, S.
Institute of Cell Biology and Neurobiology, Charité, Center for Anatomy, Berlin

66. THE FUNCTION OF THE COXSACKIEVIRUS-ADENOVIRUS RECEPTOR (CAR) IN THE DEVELOPING NERVOUS SYSTEM – ITS SELF-ASSOCIATION AND INTERACTION WITH ECM GLYCOPROTEINS
Patzke, C.; Dorner, A.; Behlke, J.; Müller, E.C.; Otto, A.; Schmidt, H.; Kröger, S.; Rathjen, F.G.
MDC, Neuronal Connectivity, AG Rathjen, Berlin

67. CORTICAL GLUTAMATE IS LINKED TO REWARD RELATED VENTRAL STRIATE ACTIVITY – A COMBINED FMRI AND 1H-MRS STUDY
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Charité Campus Mitte, Berlin

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Charité - University Medicine Berlin, Department of Psychiatry and Psychotherapy, CBF, Berlin

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Max-Delbrück-Centrum for Molecular Medicine, Physiology and Pathology of Ion Transport, Berlin

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Leibniz-Institut für Molekulare Pharmakologie, Berlin

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Max Delbrück Center for Molecular Medicine (MDC) Berlin-Buch, Function and Dysfunction of the Nervous System, Berlin

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Charite Universitätsmedizin Berlin und MDC Berlin, Cecilie-Vogt-Klinik für Neurologie, Berlin

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Humboldt University of Berlin, German Language and Linguistics, Berlin

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Faculty of Veterinary Medicine, FU Berlin, Department of Pharmacology and Toxicology, Berlin

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Physikalisch-Technische BA, AG 8.21, Berlin

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Charité, J. Mueller Institut fuer Physiologie, Berlin

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Charité, Department of Psychiatry and Psychotherapy, CBF, Berlin

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Freie Universität Berlin, Institute of Pharmacology and Toxicology, Berlin

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ECRC, Charite, Myology, Berlin

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Departement of Psychology, Humboldt University, Berlin

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Charité, Universitätsmedizin Berlin, Campus Benjamin Franklin, AG Neurophysik, Klinik für Neurologie und klinische Neurophysiologie, Berlin

89. PERFORMANCE MONITORING AND DECISION MAKING IN PATIENTS WITH BORDERLINE PERSONALITY DISORDER
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Humboldt-University of Berlin, Clinical Psychology, Berlin

90. EXPRESSION OF A CALCIUM SENSOR PROTEIN IN MICROGLIA
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MDC Berlin, Cellular Neuroscience, Berlin

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92. A MOLECULAR DISSECTION OF TRPV1 SENSITISATION USING THE NAKED MOLE-RAT
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Max Delbrück Center for Molecular Medicine (MDC) Berlin-Buch, Neuroscience, Berlin

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Charité, Institute for Cell Biology and Neurobiology, Centrum for Anatomy, Berlin

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Charité, Center for Cell Biology and Neurobiology, PRG Research Group, Berlin

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Charité, CBF, Klinik für Anästhesiologie und operative Intensivmedizin, Berlin

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Charité Universitätsmedizin Berlin, Center for Anatomy, Institute of Cell Biology and Neurobiology, Berlin

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Freie Universität Berlin, Neurobiologie, Berlin

98. ANALYSIS OF PHOSPHORYLATION TARGETS OF THE CGKI IN DEVELOPING DORSAL ROOT GANGLIA WHICH ARE IMPORTANT FOR AXON BIFURCATION IN THE SPINAL CORD
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100. PAIN ATTENUATION IN TETHERED-TOXIN TRANSGENIC MICE DUE TO REDUCED EXCITABILITY OF SENSORY NEURONS
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101. ROLE OF PRG-1 IN HIPPOCAMPAL EXCITABILITY
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Center for Anatomy, Institute of Cell Biology and Neurobiology, Berlin

104. ACUTE ALBUMIN EXPOSURE EFFECTS ARE STIMULATION FREQUENCY DEPENDENT AND SUGGEST POTASSIUM BUFFERING IMPAIRMENT
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Charité - Universitätsmedizin Berlin

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Charité, Institute for Experimental Endocrinology and Neuroscience Research Center, Berlin

106. RGS PROTEIN SUPPRESSION OF G ALPHA(O) PROTEIN-MEDIATED ALPHA-2A ADRENERGIC INHIBITION OF MOUSE HIPPOCAMPAL CA3 EPILEPTIFORM ACTIVITY
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Univ. of North Dakota School of Medicine & Health Sciences, Pharmacology, Physiology & Therapeutics, Grand Forks, North Dakota, USA

107. PERIPHERAL AND CENTRAL ORGANIZATION OF THE LATERAL LINE PATHWAY IN XENOPUS LAEVIS
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Humboldt Universität Berlin, Institute for Biology, Aquatic Bioacoustics Laboratory, Berlin

108. HYPERPHOSPHORYLATION OF TAU IN NPC-/- P301L-TAU+/+ MICE
Zonnur, S.; Goetz, J.; Ohm, T.G.
Charité, Center for Anatomy, Berlin

109. ROLE OF THE FOXP2 GENE IN PROLIFERATION AND NEUROGENESIS IN THE VENTRICULAR ZONE OF ZEBRA FINCHES, AN AREA DELIVERING NEWLY BORN NEURONS TO THE SONG NUCLEI AREA X
Steffen Schulz
Freie Universität Berlin, Institute of Biology, Department of Animal Behavior, Takustr. 6, D-15195 Berlin

110. FOXP2 TARGET GENES IN AREA X OF ZEBRA FINCHES
Iris Adam
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Abstracts of Lectures

OPTOGENETICS: DEVELOPMENT AND NEUROPSYCHIATRY APPLICATIONA SUBSET OF NATURALLY-OCCURRING

Carl Deisseroth

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A subset of naturally-occurring microbial opsin genes encode light-sensitive transmembrane ion conductance regulators (all originally characterized in non-neural systems, e.g. Hegemann et al., 1985; Kalaidzidis et al., 1998; Nagel et al., 2003; Zhang et al., 2008). If successfully adapted as a neuroscience technology, these proteins could be enormously significant, since controlling the membrane potential of targeted cell types with high temporal resolution may allow elucidation of cellular codes underlying neural circuit computation and behavior. We have now introduced to neurobiology three functionally distinct classes of these microbial opsin genes (VChR1, NpHR, and ChR2), allowing excitation with yellow light, inhibition with yellow light, and excitation with blue light, respectively. Among other crucial properties, we have found that all three operate on the millisecond timescale and can function in mammalian neurons without addition of exogenous chemical cofactors, since the chromophore for these proteins, all-trans retinal, appears to be already present at sufficient levels in mammalian brains; moreover we have addressed light and gene delivery challenges, as integrated genetic, fiberoptic, and solid-state optical approaches have provided complementary technology to allow specific cell types, deep within the brain, to be controlled in freely behaving mammals. However, technical challenges still remain, including refining tolerability, optical properties, and cell type-specific targeting. We report here on 1) molecular engineering and membrane trafficking manipulations to improve high-level expression of the opsin genes (leading to a novel eNpHR); 2) generation of redshifted excitatory optogenetic tools to allow for deeper penetration of excitation light, use of well-tolerated low-energy photons for excitation, and improved integration with existing Ca2+ indicators; and 3) improved targeting strategies to allow versatile cell type-specific expression of the opsin genes in vivo.

MOLECULAR MECHANISMS INVOLVED IN TISSUE SPECIFIC LEUKOCYTE DIAPEDESIS ACROSS THE ENDOTHELIUM

B. Engelhardt

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In multiple sclerosis and in its animal model experimental autoimmune encephalomyelitis (EAE), inflammatory cells migrate across the highly specialized endothelial blood-brain barrier (BBB) and gain access to the central nervous system (CNS). It is well established that leukocyte recruitment across this vascular bed is unique due to the predominant involvement of α4-integrins in mediating the initial contact to as well as firm adhesion with the endothelium. In contrast, the involvement of the selectins, L-selectin, E- and P-selectin and their respective carbohydrate ligands such as PSGL-1 in this process has been controversially discussed. Intravital microscopic analysis of immune cell interaction with the BBB demonstrate a role for E- and P-selectin and their common ligand PSGL-1 in lymphocyte rolling in superficial brain microvessels. However, E- and P-selectin deficient SJL- or C57Bl/6 mice or PSGL-1-deficient C57Bl/6 mice develop EAE indistinguishable from wild-type mice. Finally, although LFA-1/ICAM-1 interaction is involved in the diapedesis of leukocytes across the BBB the precise cellular pathway – transcellular or paracellular – and the respective molecluar mechanisms involved in this last step of leukocyte migration across the BBB remain to be investigated. The presentation will summarized this current knowledge in the context of a novel drug targeting α4-integrin for the treatment of relapsing-remitting multiple sclerosis targeting this process.

TOUCH, VISION AND MENTAL BODY REPRESENTATION

Patrick Haggard

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We experience our body in two quite distinct ways: as 'me' via the somatosensory systems, and as a volumetric physical object, through the visual system. This talk investigates how the brain might link visual and somatosensory information to generate a single coherent sense of one's body, of the stimuli contacting the body, and indeed of the bodily self. First, I will discuss top-down effects of visual body representation on touch. Merely viewing the body can enhance the sense of touch. Evidence from

TMS, ERP and psychophysical experiments suggests this novel form of multisensory interaction may depend on top-down visual modulation of local inhibitory interneurons in primary somatosensory areas. Second, I will consider the bottom–up transformation of primary somatosensory information into representations of external objects. Primary somatosensory representations are optimised for tactile acuity, but their striking disproportions pose a major computational challenge for the brain: how to reconstruct the true form of an external object contacting the skin from such non-uniform primary representations. I will suggest that the brain re-references primary inputs to a secondary mental representation of the body based on the true physical size of body parts. The nature and localisation of this second-level body representation, and its role in self-consciousness, are discussed.

NEURAL MECHANISMS OF SKY COMPASS ORIENTATION IN AN INSECT

Uwe Homberg

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Many insects use a celestial compass for spatial orientation and navigation. Several studies showed that insects strongly rely on the polarization pattern of the blue sky as a guiding cue but the position of the sun and the chromatic gradient in the sky offer useful information, too. To elucidate the neuronal mechanisms underlying sky compass orientation, we have analyzed the polarization vision system in the desert locust *Schistocerca gregaria*. As in other insect species, polarization vision in the desert locust relies on specialized photoreceptor cells in a small dorsal rim area of the compound eye. These photoreceptors project to dorsal rim areas in the lamina and medulla. Central processing stages for polarized light include the anterior optic tubercles, the central complex and surrounding areas in the median protocerebrum. Most neurons show polarization opponency, i.e. they receive excitatory and inhibitory input from photoreceptors with orthogonal microvilli orientations. In the anterior optic tubercle, polarized light sensitivity is combined with UV-green color coding mechanisms suggesting that these neurons code for solar azimuth by concurrent combination of signals from the spectral gradient, intensity gradient and polarization pattern of the sky (Pfeiffer and Homberg, 2007, Current Biol 17:960). In the central complex, neurons combine polarization-vision inputs from both eyes and have zenith-centered receptive fields. Single-cell recordings revealed a compass-like linear map of E-vector tunings in the columns of the protocerebral bridge, a subcompartment of the central complex (Heinze and Homberg 2007, Science 315:995). This organization suggests that the central complex computes and codes for azimuthal directions. This may be used for azimuth-dependent recognition of objects in space as well as azimuth coding during long-range navigation.

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ASTROCYTE REGULATION OF THE CEREBROVASCULATURE

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Astrocytes have recently been shown to be essential participants in the control of cerebral blood flow (CBF) through their prominent control of cerebral vessel diameter. Although the unique close relationship of astrocytes with cerebral blood vessels has long been recognized it is only within the last few years that evidence has shown how astrocytes might translate information to the vasculature on the activity level and energy demands of neurons. These findings suggest that astrocytes are key players in the system for the delivery and clearance of molecules important to brain function. Astrocytes possess the necessary signaling capability to induce both vasoconstriction as well as vasodilation in response to elevations in astrocyte endfeet Ca^{2+}. Both types of vasomotor responses are initiated by the generation of arachidonic acid (AA) in astrocytes by Ca^{2+} sensitive phospholipase A_2 (PLA_2). Subsequent to AA formation, vasoconstriction occurs as a result of the generation of 20-hydroxyeicosatetraenoic acid (20-HETE), while vasodilation ensues from the production of epoxyeicosatrienoic acid (EET) or prostaglandin E2 (PGE_2). The primary drive to increase cerebral blood flow (CBF) is enhanced neuronal activity and metabolic demands of brain tissue. However it is not known if the metabolic state of the brain itself influences the polarity of astrocyte control over the cerebrovasculature. Using two-photon Ca^{2+} imaging and uncaging as well as intrinsic nicotinamide adenine dinucleotide (NADH) imaging of single cells as a measure of redox state, we have found that the ability of astrocytes to induce vasodilations over vasoconstrictions critically relies on the glycolytic state of the tissue which is altered by oxygen (O_2) availability. Therefore the regulation of cerebral blood vessels by astrocytes is in step with the metabolic need of the surrounding brain tissue.

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IN VIVO IMAGING OF AXON REMODELING

Thomas Misgeld

Technische Universität München, Institut für Neurowissenschaften

The loss of axon branches is a shared feature of neuronal development and of neurological disease. During development, dismantling of aberrant axon branches is necessary to establish precise connectivity. Recurrence of axon loss in adult life, however, can lead to severe disability. The mechanisms that underlie physiological and pathological axon loss are not well understood, but recent data support the notion that nerve cells possess active machinery that allows them to selectively dismantle parts of their axon. In our work, we have taken advantage of in vivo microscopy of transgenic mouse lines with fluorescently labeled neurons to visualize how axons dismantle during development and after injury. In my talk, I will focus on our work on physiological axon loss at the developing neuromuscular junction, where we have identified 'axosome shedding' as a novel axon loss mechanism. I will discuss data that show that both the glial cells that surround doomed axon branches, as well as axonal transport inside these branches might contribute to final dismantling. Our data suggest that local axon branch stability is determined both by interactions between neurons and glial cells as well as by basic mechanisms of axonal resource allocation.

MODELLING OF COGNITIVE PROCESSES

Felix A. Wichmann

Technische Universität Berlin, FG Modellierung Kognitiver Prozesse

My group's goal is to understand spatial vision and, ultimately, object and scene perception on a behavioral level. Helmholtz (1867) was perhaps the first to realize that visual perception is a form of inference: visual percepts are hypotheses about the world based on incomplete sensory evidence. We strongly believe that progress towards understanding this inference necessitates the combination of psychophysical experiments and computational modelling. Currently we have three main foci: First, we want to understand the initial coding of visual stimuli, the spatial and temporal dynamics of contrast gain-control, the form of spatial filters in early vision, and how this code is adapted to the characteristics of natural stimuli. Second, we want to progress beyond early vision and thus we need to infer the critical stimulus features human observers use when perceiving complex, natural scenes. To this end we are developing non- linear system identification methods based on machine learning to estimate psychophysical perceptive fields from categorization experiments and eye-movement recordings. Third, once we have identified critical features, we want to address the fundamental problem of similarity and its relation to human categorization behavior: Can we formalize our intuitions about „similar" objects? Is there a psychological space spanned by the critical features in which stimuli are categorized as similar if they „live" close together in it? In my brief talk at the Berlin Neuroscience Forum in 2008 I will concentrate on the second issue: to estimate psychophysical „receptive" fields, so-called perceptive fields, from the fixation targets of free-viewing human observers.

Abstracts of Oral Presentations

IMPLICATIONS FROM SYSTEMATIC META-ANALYSES OF GENETIC ASSOCIATION STUDIES OF ALZHEIMER'S DISEASE AND PARKINSON'S DISEASE

Lars Bertram, MD

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Background and Aims: Alzheimer's disease (AD) and Parkinson's disease (PD) are genetically complex and heterogeneous disorders. To date, a small number of genes have been identified for both diseases causing predominantly early-onset forms with Mendelian inheritance. The majority of AD and PD cases, however, show no obvious familial aggregation and are likely governed by a variety of genetic and non-genetic factors that define an individual's risk. In the past decade, literally hundreds of reports have been published claiming or refuting genetic association between putative AD/PD genes and disease risk or other phenotypic variables, but only a handful of these potential risk factors have shown consistent effects over time.
Methods: We have created two online databases that serve as unbiased, continously updated and publicly available collections of all AD or PD genetic association studies, including genome-wide analyses. Data is collected following systematic searches of scientific literature databases, as well as the table of contents of speciality journals. For all polymorphisms

with genotype data available in at least four independent case-control samples, we routinely calculate meta-analyses based on allelic crude odds ratios from each study.
Results and Conclusions: All data and results can be retrieved online ("AlzGene": www.alzgene.org, and "PDGene": www.pdgene.org). For both diseases, a number of genetic variants have emerged to show significant risk effects in the meta-analyses. At the meeting, the most significant findings from both databases will be highlighted, with a particular focus on genes/variants that concurrently modulate the risk for both disorders, potentially indicating common denominators for neurodegeneration in AD and PD.

NEUROPROTECTION BY NOVEL ENDOGENOUS NON-HEMATOPOIETIC ERYTHROPOIETIN DERIVATIVES

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Hematopoietic cytokines have recently been identified as potent neuroprotective agents. Erythropoietin (EPO) is a glycopeptide hormone, which is primarily produced in the kidney. However, EPO is also synthesized in the brain by astrocytes, and EPO can protect neurons from damage in various models of neurological disorders. Unfortunately, clinical use of EPO as a neuroprotectant is complicated by its hematopoietic effects.We have identified endogenous EPO derivatives without hematopoietic activity. In contrast to EPO, these EPO derivatives failed to stimulate erythropoiesis in clonogenic progenitor assays. However, both EPO and its derivatives protected cultured rat neurons from oxygen-glucose deprivation (OGD), an *in vitro* model of ischemia. EPO derivatives also protected H9C2 cardiomyocytes from OGD-induced cell death, suggesting that they have a more general cytoprotective potential. We characterized the pharmacodynamics of EPO and its derivatives in vitro. Our data suggest that EPO derivatives are powerful neuroprotective agents, which share EPO's cytoprotective effects, but do not show the undesirable side-effect of promoting hematopoiesis.

A TETHER LINK REQUIRED FOR TOUCH

Jing Hu, Li-Yang Chiang, Bettina Erdmann & Gary R. Lewin

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Genetic analysis of touch sensation in C. elegans and research on mechanosensitive hair cell in inner cochlea have suggested the existence of an extracellular link which tethers the mechanosensitive ion channels to matrix and transduces mechanical force to the channels (Ernstrom & Chalfie. 2002. Annu Rev Genet 36: 411-53; Syntichaki & Tavernarakis. 2004. Physiol Rev 84(4) 1097-153). So far there is no evidence showing whether in mouse an extracellular link is essential for mechanotransduction (Lewin & Moshourab. 2004. Neurobiol 61(1): 30-44). Recent evidence suggests that mechanotransduction components and mechanisms are conserved between C. elegans and mammals (Wetzel, Hu et al. 2007. Nature 445(7124): 206-9). In the past few years we have been working intensively to address the question whether extracellular link is also conserved in mouse mechanosensation. We have demonstrated that, as in C. elegans and Drosophila, an extracellular link is essential for mechanotransduction in mouse sensory neurons. We have also found that cleaving this link with a serine endopeptidase-subtilisin could immediately and reversibly abolish the mechanosensitivity of sensory neurons. This cleavage and regeneration of the extracellular link could be clearly observed using TEM (Transmission electron microscopy). This is the first evidence to show that the extracellular link of mechanotransducer exists and is essential for mechanosensation.

DIFFERENTIAL MECHANISMS UNDERLYING ALTERED NEURONAL EXCITABILITY FOLLOWING BLOOD-BRAIN BARRIER DISRUPTION

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Perturbations in the integrity of the blood-brain barrier have been reported in both humans and animals under numerous pathological conditions. Although the blood-brain barrier prevents the penetration of many blood constituents into the brain extracellular space, the effect of such perturbations on the brain function and their roles in the pathogenesis of cortical diseases are unknown. In our work we established a model for focal disruption of the blood-brain barrier in the rat cortex by direct application of bile salts. Exposure of the cerebral cortex in vivo to bile salts resulted in long-lasting extravasation of serum albumin to the brain extracellular space and development of a focus of epileptiform discharges within 4-7 d after treatment. We found that application of serum albumin to the cortex induced similar hyperexcitability without opening the BBB. Exposure of the cortex to serum albumin is associated with albumin uptake into astrocytes, which is mediated by transforming growth factor beta receptors (TGF-betaRs). This uptake is followed by marked astrocytic activation and an

altered pattern of astrocytic gene expression, as seen in microarray and rt-PCR analysis. We investigated the functional implications of altered expression of genes critically involved in the regulation of neuronal excitability. Both, astrocytic potassium buffering and glutamate clearance were compromised and affected neuronal function. To discriminate the effect of the two systems separately we used a neuron model and varied both potassium and glutatmate clearance. While reduced potassium clearance lead to marked EPSC facilitation in stimulation trains, slowed glutamate time constants had the opposite effect. However, both mechanisms together show a synergistic effect, leading to maximal EPSC facilitation maximal at stimulation frequencies of 10 Hz. Recordings from brain slices exposed to albumin confirmed this frequency range. Our data suggests a crucial impact of astrocytic dysfunction on neuronal excitability and epileptogenesis following cortical albumin exposure.

MITOCHONDRIA AND NEURONAL ACTIVITY: INSIGHTS FROM THE HEALTHY AND THE EPILEPTIC HIPPOCAMPUS

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Mitochondria are central for various cellular processes that include ATP production and intracellular Ca^{2+} signalling. Neurons critically depend on mitochondrial functions to establish membrane excitability and to execute the complex processes of neurotransmission and plasticity. While much information about mitochondria is available from studies on isolated mitochondria and dissociated cell cultures, less is known about mitochondrial functions in intact neurons in brain tissue. In the recent years, my group has studied mitochondrial functions during neuronal activity in slice preparations from the healthy and the epileptic hippocampus by combining electrophysiological and imaging techniques. We provide evidence 1) that there is a fine-tuned coupling of neuronal activity and mitochondrial redox responses (energy metabolism), 2) that rapid mitochondrial Ca^{2+} transients represent one of the main determinants for neurometabolic coupling, 3) that complex neuronal network activities such as gamma-oscillations are highly sensitive to decreases in pO2 and concomitant changes in mitochondrial redox state, and 4) that the tight coupling of neuronal activity and mitochondrial functions has devastating consequences in epilepsy, which include Ca^{2+}-mediated mitochondrial depolarization in neuronal dendrites and somas, formation of reactive oxygen species (ROS) and subsequent metabolic dysfunction due to mitochondrial DNA and enzyme damage. Our studies highlight the importance of a functional understanding of mitochondria during activities of individual neurons and neuronal networks in health and disease.

A VICIOUS CYCLE INVOLVING RELEASE OF HSP60 FROM INJURED CELLS AND ACTIVATION OF TLR4 MEDIATES NEURODEGENERATION IN THE CNS

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Infection, ischemia, trauma, and neoplasia elicit a similar inflammatory response in the central nervous system (CNS) characterized by activation of microglia, the resident CNS monocyte. The molecular events leading from CNS injury to the activation of innate immunity is not well understood. We show here that the intracellular chaperone heat shock protein 60 (HSP60) serves as a signal of CNS injury by activating microglia through a toll-like receptor 4 (TLR4)- and myeloid differentiation factor 88 (MyD88)- dependent pathway. HSP60 is released from CNS cells undergoing necrotic or apoptotic cell death and specifically binds to microglia. HSP60-induced synthesis of neurotoxic nitric oxide by microglia is dependent on TLR4. HSP60 induces extensive axonal loss and neuronal death in CNS cultures from wild type but not TLR4 or MyD88 loss-of-function mutant mice. This is the first evidence of an endogenous molecular pathway common to many forms of neuronal injury that bi-directionally links CNS inflammation with neurodegeneration.

ALTERATIONS IN NEUROMETABOLIC-NEUROVASCULAR COUPLING BY CORTICAL SPREADING DEPRESSION IN RAT SOMATOSENSORY CORTEX

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The mechanisms of activity induced changes in cerebral blood flow (CBF) and metabolism are incompletely understood. We tested the hypothesis that the relationship between evoked changes in neuronal activity, oxygen consumption and CBF is variable and can be changed by cortical spreading depression (CSD). We investigated the effect of cortical spreading depression on functional activation induced (forepaw stimulation) changes in neuronal activity, rCBF and regional blood oxygenation (rCHO; oxy-, deoxyhemoglobin concentration) by SEP recordings, laser-Doppler flowmetry and optical hemoglobin spectroscopy in rat somatosensory cortex. Averaged responses prior to CSD were compared with blocks of averaged responses up to 1.5h after CSD. Baseline rCBF was transiently (~60

min) reduced after CSD. This was accompanied by an increase in deoxy-hemoglobin (Hbr) and decrease of oxy-hemoglobin (Hbo). Before CSD, activity induced Hbr showed a well known isolated decrease and Hbo changes were monophasic increases, which followed the rCBF changes during activation. After CSD, rCBF responses and SEP were significantly attenuated but tend to recover over time. The impact of CSD on evoked rCHO responses was heterogeneous. Hbr responses ranged from biphasic increase-decrease patterns to entirely positive responses. At the same time Hbo increases were significantly attenuated, despite the recovering CBF response. Together, the individual parameters showed a different recovery pattern after CSD and suggest a change in the underlying energy metabolism during activation.The observed divergent modification of activity induced changes in rCBF, neuronal activity and blood oxygenation by a single CSD indicates a long term (90 min) impairment of neurometabolic-vascular coupling and suggests a variable relationship between neuronal activity and oxygen consumption, influenced by pathophysiological events.

PIGMENT EPITHELIUM DERIVED FACTOR DURING POSTNATAL DEVELOPMENT, AGEING AND DISEASE OF THE NERVOUS SYSTEM

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Pigment Epithelium Derived Factor (PEDF) is a secreted glycoprotein which possesses multiple and varied biological properties, it is neurotrophic, neuroprotective, antitumorigenic and has a potent antiangiogenic activity. We have focused our attention on exploring the specific localization, function and effects of PEDF on the nervous system during normal development, aging, and disease. The following is a brief account of some of our results. We have demonstrated that PEDF protein is naturally down regulated with age in the roedent eye and brain, leading to an increased VEGF/PEDF ratio with age. This suggests a potential higher risk for neovascularization and partly the cause of some degenerative diseases at older stages of life in these organs. With Immunohistochemistry and cell specific double labeling we have shown the specific expression of PEDF in endothelial cells and neurons in various regions of the adult brain. This defined localization of PEDF open the possibility to search for other relevant effects of this factor in the brain. Our in vivo results show that intraventricular infusion of PEDF has a stimulatory influence on subventricular zone neural stem cells while reducing the proliferation of microglia cells in the traumatic injured brain. These results support the importance of this molecule in the control of neurogenesis and inflammation in the lesioned brain and indicate the significant therapeutic potential that PEDF might have for the diseased nervous system.

A CGMP SIGNALING PATHWAY ESSENTIAL FOR SENSORY AXON BIFURCATION

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Axonal branching is a prerequisite for the formation of the complex wiring pattern of the mature nervous system E.g. the central trajectories of dorsal root ganglion axons display at least two types of ramifications when they enter the spinal cord: (1) bifurcation at the dorsal root entry zone (DREZ) and (2) interstitial branching from stem axons to generate collaterals that penetrate the grey matter. The signaling cascades that underlie axonal branching *in vivo* have remained poorly understood thus far.

We report a cGMP signaling cascade critically involved in the establishment of the highly stereotyped pattern of T-shaped axon bifurcation of sensory axons at the DREZ of the spinal cord. Single axon labeling using DiI revealed that embryonic mice with an inactive receptor guanylyl cyclase Npr2 or deficient for cGMP-dependent protein kinase I (cGKI) lack the bifurcation of sensory axons at the DREZ, i.e. the ingrowing axon either turns rostrally or caudally instead. Cross-breeding experiments of these mutant mice with a mouse line expressing EGFP in sensory neurons under control of the Thy-1 promoter demonstrate that the bifurcation error is maintained to mature stages. In contrast, interstitial branching of collaterals from primary stem axons remains unaffected.

At a functional level, the distorted axonal branching is accompanied by reduced synaptic input, as revealed by patch clamp recordings of neurons in the superficial layers of the cord. Hence, our data demonstrate that a cGMP signaling cascade including Npr2 and cGKI is essential for axonal bifurcation at the DREZ and influences neuronal connectivity in the dorsal spinal cord.

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Schmidt H, Stonkute A, Jüttner R, Schäffer S, Buttgereit J, Feil R, Hofmann F, Rathjen FG (2007) The receptor guanylyl cyclase Npr2 is essential for sensory axon bifurcation within the spinal cord. J Cell Biol. 179: 331-340.

GENETIC DISSECTION OF SELENOPROTEIN FUNCTIONS IN NEURONAL FUNCTION AND SURVIVAL

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Selenoproteins (SePs) are a small, but significant, class of proteins containing the rare amino acid, selenocysteine (Sec). Although the functions of many SePs are still unknown, there is compelling evidence that SePs carry out redox reactions like seleno-enzymes of the glutathione peroxidase (Gpx) and thioredoxin reductase (Txnrd) gene families. The brain contains low amounts of selenium (Se), but can maintain its Se content even during prolonged Se deficiency. Therefore, it is practically impossible to create an experimental model for brain Se deficiency. However, when we inactivated the selenoprotein P (SePP) gene, we destroyed the mechanism of brain Se retention. Accordingly, Sepp-KO mice are highly dependent on dietary Se uptake and suffer from neurodegeneration and epilepsy at normally adequate dietary Se content. In an attempt to delineate which cerebral cell type depends most on SeP expression, we created mice with neuron-specific ablation of the gene encoding tRNASec, thus preventing entirely SeP biosynthesis. Mice lacking neuronal SeP biosynthetic capacity suffer from massive neurodegeneration in hippocampus and cerebral cortex from their second week of life. In culture, these neurons die even in the presence of added antioxidants, suggesting that SePs mediate more than redox-control. We then genetically dissected which single selenoproteins are necessary for neuronal function. While Gpx4 proved to be an indispensable gene, lack of Txnrd1 in neurons did not cause neurological dysfunction. Recently, lipoprotein receptors (LRPs) have been identified as receptors mediating SePP uptake. We found that neurodegeneration observed in LRP-deficient mouse models depends on dietary Se content raising the possibility that compromised LRP function – as observed in Alzheimer's diesease – is not primarily caused by disturbed cholesterin traffic, but by impaired Se uptake into the brain.

C-MAF IS AN IMPORTANT REGULATOR OF MYELINATION IN THE PERIPHERAL NERVOUS SYSTEM

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The proto-oncogene c-Maf is a transcription factor of the basic-region leucine zipper (bZIP) family. c-Maf is known to control the differentiation of T cells, chondrocytes and the lens. c-Maf is also expressed in the central and peripheral nervous system, but its functions in neural cells have not been assessed. We performed a detailed analysis of c-Maf expression in the nervous system, and observed that c-Maf is expressed in glial cells of the peripheral nerves, and in a subset of sensory neurons. In Schwann cells, c-Maf expression is first detected around E18 and is maintained in the adult. c-Maf expression is thus initiated at the time Schwann cells start to myeliniate, and expression is observed in myelinating, but not in non-myelinating Schwann cells. c-Maf mutant mice die shortly after birth. To investigate by genetic methods the function of c-Maf in the peripheral nervous system, we introduced a targeted mutation using the Cre/loxP system and generated Wnt1-Cre//c-Maf mutant mice; such animals are viable. We observed in these mutant mice a pronounced reduction in the myelin thickness of peripheral nerves. This hypomyelination was accompanied by the formation of tomaculae at the nodes of Ranvier. In addition, the mutation of c-Maf leads to a reduced conduction velocity of peripheral nerves. Despite this pronounced changes in myelination, we did not observe a change in the expression of myelin genes. Our results demonstrate that c-Maf is an important factor in the transcriptional network regulating myelination in the peripheral nervous system.

Poster Session I

Thursday, June 5, 15.35 - 17.00
Friday, June 6, 10.00 - 11.00

1 DETECTION OF SIGNALING PATHWAY ACTIVATION IN RAT DRG-NEURONS BY AUTOMATED RELATIVE IMMUNOFLUORESCENCE

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Posttranslational modifications are key to regulation of protein activity and can therefore be taken as surrogate measurement for the activity status of signaling proteins such as kinases. This is done routinely by the use of phospho-specific antibodies in Western-Blot analysis or ELISAs. We now established in our laboratory a microscopy technique, which analyses the activation status based on single cell measurements in cultures of dissociated dorsal root ganglia from adult rats. For automatic identification of neurons with an automated "Axioplan 2 imaging" (Zeiss) microscope controlled by the software "Metacyte" (MetaSystems), we optimised parameters describing form and size of neuronal cell bodies. Technical sources of variation such as bleaching and heterogeneous illumination of the view field were minimized. Then, the immunofluorescence intensity derived from fluorophore-coupled phosphorylation specific antibodies against signaling proteins was measured in every single neuron. Comparing data from untreated and treated cultures, we were able to follow induction of activation of the mitogen activated kinases Erk1/2 and JNK as well as of the epsilon isoform of protein kinase C. The activation of these signaling pathways is known to be involved in sensitization of nociceptive neurons. Therefore, this technique opens the door to automated immunofluorescent investigation of heterogenous cell systems such as nociceptive neurons evaluating qualitatively for colocalization of proteins and/or signaling events as well as quantitatively for the magnitude of activation of signaling cascades.

2 DEVELOPMENT OF GENETIC TOOLS FOR SELECTIVE AND REVERSIBLE SILENCING OF ION CHANNELS USING NATURAL TOXINS

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Venomous animals produce an enormous number of different peptide toxins which often show a high affinity for specific ion channels and receptors. Numerous of toxins from cone snails and snakes have been reported to be selective as well as potent blockers of specific subtypes of ion channels (Albuquerque et al., 1997; Bowersox and Luther, 1998; Nicke et al., 2003, 2004). Recently it has been shown that these toxins retain their ability to block ligand and voltage-gated receptors and ion channels in Xenopus oocytes and in zebrafish when tethered to the cell surface via a GPI membrane anchor (Ibanez-Tallon et al., 2004). These toxin fusion constructs allow the genetic and cell-autonomous block of specific subsets of ion channels and receptors after being expressed in the target cell. Our work combines the lentiviral system for tethered toxin delivery to the target cells and a tet-KRAB based, doxycycline inducible regulation of expression (Szulc et al., 2006), which together allow the specific and also reversible silencing of receptor and ion channel subpopulations in a cell-autonomous manner. To date we are testing several different versions of tethered constructs with toxins targeting voltage gated $Ca2^{+}$-channels and nicotinic acetylcholine receptors on their functionality *in-vitro* in neuronal cultures as well as *in-vivo* in mice. In the future this new approach could be used to inhibit specific currents in different brain regions and could lead to more insight into the circuitory complexity of the brain, the way of information processing and the particular contribution of single ion channel or receptor subtypes.

3 A MODEL OF NEURONAL COLOR CODING AND COLOR SENSATIONS IN MAN

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Light entering the eye causes color sensations. The elemental sensation spots consist of mixtures of the six elementary color (EC) sensations red, green, blue yellow, black, and white [1] of the respective amounts, which are adequately detailed by the psychophysical EC model. The neuronal color coding (CC) system is well described by the physiological CC model including physiological models of human cones [2]. The combined CC/EC model predicts the amounts of elementary colors from the spectral light intensity distribution alone.

Classical psychophysical measurements [3] of the amounts of EC sensations, stimulated by monochromatic light, were simulated with the CC/EC model. Best fits of predicted data to data measured in two individual observers allowed for the unique determination of the parameters. It turned out that the color vision system of observer II was most usual. Whereas observer I showed to possess an unusual blue/yellow color opponent coding (COC) neuron type, with two swapped excitatory and inhibitory synapses. This result clearly demonstrates that the CC/EC model [4] enables even the identification and localization of individual differences in neuronal color coding systems that are classified to be normal trichromatic.

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4 SODIUM CURRENTS IN IMMORTALIZED AND DEVELOPING STRIATAL PROGENITOR CELLS

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Na^+ currents (I_{Na}) as key players in neuronal development have been studied in 3 different sets of developing rat striatal cells: (1) immortalized at embryonic day 14 (SV40 large T antigen transformed ST14A) and short term cultured (2) at E14 and (3) at P0, using whole-cell patch-clamp, molecular and immunocytochemical approaches. To investigate the presence of voltage gated sodium channels we stained with a panNav antibody which confirmed the ubiquitous presence and no differential distribution in all groups. However, in proliferating ST14A cells functional INa was only present when held substantially hyperpolarised (-120 mV) in 26 out of 31 cells and irrespective of cell fate. I_{Na} activated with a $V_{1/2}$ of -32 mV and showed a fast time- and voltage-dependent activation and full inactivation. At a more physiological holding potential of -70 mV less I_{Na} was available (8/51) due to a remarkably hyperpolarised steady state inactivation. INa in ST14A cells was TTX resistant. Current clamp experiments showed that I_{Na} can be recruited from a membrane potential below –90 mV and produce action potential like responses. E14 and P0 striatal cells showed currents with similar kinetics, but a remarkable difference in availability and voltage dependence of activation of sodium channels and in their TTX sensitivity. The peculiarity in ST14A might be explained by a relative overweight of "heart" $Na_V1.5$ and especially its splice variant NaV1.5a as suggested by RT-PCR. We conclude that Na^+ channels are in the membrane of embryonic and early postnatal striatal cells, but they remain quiescent by a transcriptional mechanism. Alternative splicing plays a role in regulation of functional I_{Na} and in the control of developmental state.

5 ALCOHOLISM MEDIATES ASSOCIATION BETWEEN STRIATAL REWARD PROCESSING AND IMPULSIVENESS

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Alcoholism can be described as a well learned behavioral pattern, which is based upon biological, social and psychological factors. On a neurobiological level it may be connected with impairments of the dopaminergic mesolimbic reward system. Furthermore alcoholism might be accompanied by altered personality factors like impulsiveness. Here we investigate the linkage between alcoholism, dysfunction in mesolimbic reward system and impulsiveness. Using functional magnetic resonance imaging (fMRI) we investigated detoxified male alcoholics and age-matched healthy controls during a monetary incentive delay task (MID). In this task, visual cues predicted that a rapid response to a subsequent target stimulus would result in monetary gain, avoidance of monetary loss or no consequence. Additionally the association with impulsiveness was assessed using the Barratt Impulsiveness Scale (BIS). Alcoholics scored significantly higher on the BIS than controls. Healthy controls showed a significantly stronger activation of ventral striatum than alcoholics during both anticipation of gain and loss. Additionally, in controls, BOLD response in putamen during gain anticipation was negative correlated with impulsiveness. In contrast, higher impulsiveness was associated with stronger BOLD response in putamen, anterior cingulate and inferior frontal gyrus during anticipation of loss in alcoholics. These results support the notion of a dysfunction in the reward system in alcoholics and elevated impulsiveness scores in these patients. Furthermore the negative correlation between activation in putamen during reward anticipation and impulsiveness in healthy controls was not observed

in alcoholics. Instead, in alcoholics we found a positive correlation between activation in putamen during loss anticipation and impulsiveness. These findings suggest that alcoholism per se mediates the relationship between reward processing and impulsiveness.

6 ROLE OF EXTRACELLULAR SIGNAL-RELATED KINASE 1 IN THE REGULATION OF NEUROINFLAMMATION

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Extracellular signal-related kinases (Erk) are mitogen-activated protein kinases (MAPK) that are not only involved in T cell activation but are also known to be conversely involved in the induction of T cell anergy. Activation of the T cell receptor triggers amongst others the Ras/Raf/MEK(MAPK Erk Kinase)/Erk pathway that controls the cell cycle machinery. We have shown that the 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor atorvastatin induces a sustained phosphorylation of Erk1 that is rather necessary for atorvastatin-induced T cell anergy in vitro. To determine the role of Erk1 in the induction of peripheral tolerance in vivo we have induced EAE (experimental autoimmune encephalomyelitis) in $Erk1^{-/-}$ C57BL/6 transgenic mice with a myelin oligodendrocyte glycoprotein peptide (MOG_{35-55}). We show that Erk1 is important in regulating the progression of the disease as shown by an increased severity and earlier development of symptoms in the $Erk1^{-/-}$ mice. To dissect the role of Erk1 within the immune versus the central nervous system we applied bone marrow chimeras. For this we reconstituted sublethally irradiated C57BL/6-CD45.2 mice with bone marrow cells of $Erk1^{-/-}$ or $Erk^{+/+}$ (wildtype littermate) C57BL/6-CD45.1 mice or alternatively reconstituted sublethally irradiated $Erk^{1-/-}$ or $Erk^{+/+}$ (wildtype littermate) C57BL/6-CD45.1 mice with bone marrow cells of C57BL/6-CD45.2 mice. After a minimum of 8 weeks we have induced EAE. From these experiments we could clearly show that Erk1 plays a predominant role in regulating an immune response, as shown by a dramatic increased disease severity in mice with an immune system deficient of Erk1. All together these results indicate the significance of Erk1 in regulating immunological processes that ultimately lead to neuroinflammation and signal the importance of therapeutically targeting this MAPK for the treatment of autoimmune diseases.

7 CLC-2 CL- CURRENTS IN OLIGODENDROCYTES FROM ACUTE SLICES IN THE MOUSE CORPUS CALLOSUM

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Chloride channels have several roles in cellular physiology including the control of water flux across the membrane and cell volume regulation. In a recent study, Blanz et al. (2007) showed that the white matter of the brain and spinal cord of ClC-2 knock-out mice developed widespread vacuolation between myelin sheaths. ClC-2 is known to be expressed in astrocytes and neurons, but expression in oligodendrocytes has not been reported. We therefore recorded membrane currents with the patch-clamp technique from oligodendrocytes in mouse corpus callosum in acute slices. Oligodendrocytes were identified by their typical morphology after injection with fluorescent dye trough the electrode and their characteristic current profile. The cells had parallel processes in the orientation of axons tracts and currents elicited by de- and hyperpolarizing voltage steps showed fast decay and symmetrical tails as previously described (Berger et al. 1991). To block the cationic components of membrane currents and isolate the ClC-2 current we substituted Na^+ and K^+ with NMDG and Cs^+ in the extra- and intracellular solutions. In whole cell configuration, after dialysis, we stably recorded an inwardly rectifying, not inactivating current with a slow activation kinetic. This current was reversibly blocked by to 300μM Cd^{++}. These results are similar as previously reported for astrocytes (Makara et al. 2003). This current component could not be recorded in oligodendrocytes from ClC-2-KO mice. We conclude that oligodendrocytes express functional ClC-2 which seems to be important for the maintenance of myelin.

8 SYNERGISTIC EFFECTS OF IL-4 AND IL-10 ON AXONAL OUTGROWTH AND REINNERVATION

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Controversial debate continues as to whether T cells are able to promote central nervous system (CNS) repair. Evidence suggests that T-helper cells type 2 (Th2) play a beneficial role in the context of CNS injury. Recently, we could demonstrate that Th2 cells promote axonal regeneration and functional recovery after CNS injury via perilesional delivery of interleukin-4 (IL-4). Here, we investigated the interaction of IL-4

and IL-10 in axonal outgrowth and regeneration in organotypic brain slices. Murine entorhinal cortex (EC) explants from p2 mice were embedded in a three dimensional collagen matrix. Axonal outgrowth was analyzed after administration of IL-4, IL-10 or a combination of the two compared to untreated controls. To more accurately analyze outgrowth in an in vivo context, we also tested the influence of these cytokines on the reinnervation of the denervated target area by employing an organotypic co-culture model of enhanced green fluorescent protein (EGFP)-transgenic ECs and hippocampi. Using these models, we were able to show that IL-4 and IL-10 synergistically promote axonal outgrowth and reinnervation in organotypic brain slices. Furthermore, IL-10-induced axonal outgrowth of organotypic brain slices is abolished in slices derived from IL-4 receptor-deficient mice, while IL-4 secreted by transfected fibroblasts did not promote axonal outgrowth in the absence of IL-10. These data suggest, that IL-10-induced axonal outgrowth is dependent on IL-4 receptor signaling.

9 MIGRATION OF GENE-MODIFIED BONE MARROW-DERIVED CELLS INTO MOUSE RETINAS

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Bone marrow-derived cells (BMDCs) have been suggested as a delivery system for gene therapy in retinal degenerations. The potential of BMDCs for transferring a therapeutic gene into the CNS is yet controversial. To study the migration of BMDCs into the retina, EGFP-expressing BMDCs were systemically transplanted into lethally irradiated C57BL/6 recipients. Irradiation-induced functional and morphological changes of the retina were estimated at 5 and 12 weeks post-BM transplantation (pBMT) by scanning laser ophthalmology (SLO) and electroretinography (ERG). The time-dependent induction of cytokine and chemokines in the irradiated eyes was determined over 12 weeks pBMT. Chimeras were killed at 1, 2, 4, 12, 32, 44 and 60 weeks pBMT. The retinas were analysed by immunohistochemistry. To prove the efficacy of BMDCs for gene delivery into the retina, retrovirally transduced BMDCs expressing EGFP were transplanted to lethally irradiated mutant recipients with retinal degenerations (SCA7 and FVB/N). The retinas were analysed at 8 and 12 months pBMT. Over 3 months pBMT, irradiation-induced functional and morphological alterations of the retina were not significantly observed. The induction of chemokine and cytokine appears to coincide with the appearance of EGFP-expressing microglia in the eyes. EGFP-expressing cells in retinas were identified as microglia based on morphology and immunophenotype. The number of GFP-expressing retinal microglia was not significantly changed after 32 weeks pBMT. In mutant retinas, gene-modified BMDCs were found to persist for up to 1 year pBMT with a stable expression of EGFP from a retrovirus. Taken together, BMDCs may be used as vehicles for gene delivery to the retina.

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10 MECHANISMS AND FUNCTIONAL ROLE OF IMMUNE RESPONSE FOLLOWING AXONAL LESION

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ECL-induced brain damage does not involve a typical adaptive immune response. However, ECL leads to the activation of microglia migrating to the zones of axonal degeneration where they act as immunophenotypically antigen-presenting cells (MHCII+, CD86+, CD80-) and come into close contact with infiltrating T cells. It has been observed that initial expansion of myelin-specific T cells and subsequent inflammation in regions of axonal degeneration are transient and presumably regulated, implying an active maintenance of immune tolerance. We have found that mice pre-treated with ECL 30 days before EAE induction show a reduced EAE disease severity, indicating that an immune response triggered by traumatic injury may induce regulatory immune mechanisms. Moreover we could show that microglia induce regulatory T cells in an antigen-specific manner *in vitro*. Furthermore, traumatic CNS injury such as ECL induces an increased number of regulatory T cells in the brain in a time-dependent fashion *in vivo*.Taken together, these data suggest that microglia are involved in the development and induction of regulatory immune mechanisms in the context of CNS trauma. Elucidating the role of microglia-primed T cells in CNS trauma may lead to a better understanding of general mechanisms in neuroregeneration.

11 B56ß INTERACTS WITH CALEB/NGC AND INHIBITS CALEB/NGC-MEDIATED DENDRITIC BRANCHING

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The development of dendritic arbors is essential for neuronal information processing, but the underlying

mechanisms are currently not well understood. The importance of transmembrane proteins for connecting extrinsic cues, which regulate dendrite formation, to intracellular mediators of cytoskeletal rearrangements has been highlighted during the last years. Recently we demonstrated that CALEB/NGC (Chicken Acidic Leucine-rich EGF-like domain containing Brain protein/Neuroglycan C), a neural member of the EGF family, is a critical mediator in the formation of dendritic tree complexity by enhancing dendritic branching. Here we show a more detailed characterization of the mechanisms underlying CALEB/NGC-induced dendritic branching. Extracellularly, the EGF-like domain of CALEB/NGC is necessary and sufficient for stimulating dendritic arborization. In a screen for novel interaction partners of CALEB/NGC, which functionally link this transmembrane protein to the phosphatidylinositide 3-kinase-Akt-mammalian target of rapamycin pathway, we identified B56ß, a regulatory subunit of protein phosphatase 2A, as a candidate that negatively regulates CALEB/NGC-induced dendritic branching.

Literatur:
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12 LATERAL LINE RESPONSES INTEGRATE THE WAVE CURVATURE

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Xenopus laevis uses a mechano-sensory lateral line system for localizing prey on the water surface. About 180 water-velocity sensitive organs ('stitches') are systematically distributed at the frog's body and encode wave signals. Excitation patterns across these stitches are used to compute wave source representations in the CNS. In this study the effects of the wave curvature on the responses in the CNS were investigated. Three wave sources were placed in 4.5, 6.75 and 9 cm (corresponding wave curvatures were 22.2, 14.8 and 11.1 m^{-1}). Standardised stimulus paradigms were used and wave amplitudes and spectral composition were stabilized at the frog's centre. 98 responses to surface wave stimuli were extracellularly recorded. Wave frequencies eliciting best response peaked at 30 Hz (26% of all units). Stimulation of the frog from various distances (resulting in variable wave curvatures) with stabilized surface waves (in terms of amplitude and frequency) elicited significant curvature-dependent response rates for 60 of 98 central LL-units ($p<0.05$; Wilcoxon-test). 75% of these units displayed a response-rate change $\geq$50% when stimulated from the 3 source distances. 8 out of 38 LL-units showed no distance-sensitivity based on response-rate but phase coupling for a subset of wave sources only (Rayleigh test, $p<0.05$; $VS>0.03$). Combined, 69% of the 98 recorded units showed changes in there response rate or their VS and were considered as distance sensitive. Additional studies were initiated to investigate the influence of different stimulation angles on the responses in the CNS. Two sets of wave sources (3 distances each) were placed at 90° and 0° relative to the frog's rostro-caudal axis. Of 8 recorded distance sensitive units, 6 exhibited the same trend in their rate-curvature functions at both stimulation angles – suggesting stable distance coding might occur in the CNS based on wave curvature.

13 DYSFERLIN DEFICIENT MUSCULAR DYSTROPHY FEATURES AMYLOIDOSIS

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Objectives: Dysferlin is widely expressed and has been implicated in diseases such as multiple sclerosis and Alzheimer disease. Mutations in the dysferlin gene *(DYSF)* cause muscular dystrophy (LGMD2B, Miyoshi-myopathy). The consequences of *DYSF* mutations on protein structure are poorly understood.
Methods: The gene encoding dysferlin was sequenced in patients with suspected dysferlin-deficient muscular dystrophy. Muscle biopsy specimens were analysed by histochemistry, immunohistochemistry and electron microscopy. Antibodies against N-terminal dysferlin-peptides were raised.
Results: In three families with homozygous or compound heterozygous *DYSF* mutations widespread amyloid deposits were detected in skeletal muscle. Known causes of amyloidosis were excluded and dysferlin was identified as a main constituent of the amyloid deposits. Mutations in *DYSF* leading to amyloid are all located within the same region of the gene.
Conclusions: LGMD2B is the first muscular dystrophy associated with amyloidosis and dysferlin is a new amyloidogenic protein.

14 ROLE OF $G_{ALPHA-I-2}$ ON ZO-1 UNDER EPINEPHRINE STIMULATION

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The blood-brain-barrier permeability in several brain pathologies is increased, leading to complications and decreasing survival. Tight Junctions (TJ) are protein complexes in endothelial/epithelial cell membranes attaching cells to each other, sealing the paracellular cleft and regulating its permeability. The scaffolding protein of TJ is ZO-1. Its SH3 and GuK domains form a functional SH3-hinge-GUK unit (ShG) that binds other junctional proteins and can be phosphorylated. TJ are indirectly regulated by G-protein-signaling cascades: $G_{\alpha 0}$ and $G_{\alpha i2}$ may increase TJ biogenesis and paracellular tightness respectively, and a constitutively active mutant of $G_{\alpha 12}$ reduces the paracellular tightness. We propose a direct binding of $G_{\alpha i2}$ to the ShG unit of ZO-1. HEK-293 cells were cotransfected with CFP-Gi2 and one of the following: ZO-1(ZO1YFP), C-terminal-truncated ZO-1($ZO1^{17\text{-}899YFP}$) or ShG($YFPZO1^{520\text{-}809}$). After 72 h, the cells were incubated in 5, 50 and 500μM epinephrine for 10 min, and fixed for LSCM analysis. Same cotransfections were spectrofluorometrically assayed for FRET. Our preliminary data show that after cotransfection with CFP-$G_{\alpha i2}$ the ZO1YFP expression is enriched at the cell-cell contacts acquiring an epithelial-like pattern. Under 5 μM epinephrine, Gi2 shifts its intracellular distribution from the cytosol to the submembranal space colocalizing with ZO1YFP. Partial colocalization with $ZO1^{17\text{-}899YFP}$ and $YFPZO1^{520\text{-}809(ShG)}$ is always observed, but is increased after 5 μM epinephrine stimulation. The fluorescence spectra under non-stimulating conditions showed mild FRET in all cases, but their efficiency increased after 5μM epinephrine stimulation. These results suggest that Gi2 can bind directly to the ShG unit of ZO-1 and might facilitate membrane localization of ZO-1, probably representing a first-response modulator of TJ, triggered after cell stress or pharmacological intervention.

15 PERSONALITY TRAITS AND STRUCTURAL BRAIN ALTERATIONS IN HEALTHY SUBJECTS: A MORPHOMETRIC ANALYSIS OF MRI-DATA

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Various neuroimaging studies draw an association between genetics, personality and structural brain alterations. For example, surveys examining normal fear conditioning or psychiatric disorders (e.g. anxiety disorders, mood disorders) demonstrated a genetically driven fear-processing network, involving subcortical structures and prefrontal neocortical areas. Identifying such associations in healthy subjects might help to understand human behavior and may help in the early detection and treatment of mental disorders. This investigation aimed for the detection of such specific processing patterns determined by personality traits, behavioural parameters and genetic predispositions. We examined the correlation between gray matter volume on a voxel-by-voxel basis using high-resolution T1-weighted magnetic resonance image (MRI) and optimized voxel-based morphometry (VBM) analysis and personality parameters, such as anxiety, sensation seeking, neuroticism in healthy subjects in fourty-six healthy subjects. Major personality traits were correlated with gray matter volume in the prefrontal and orbitofrontal lobe suggesting a key role of the frontal lobe in behavioral control and social competence. Gray matter volume of additional cerebral regions showed significant correlations with personality traits indicating a broad neuronal network involved in normal human behavior. Furthermore, the impact of genetic variations of neurotransmitter systems implicated in behavioral modulations on cerebral morphometry will be presented.

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16 AMEBOID MICROGLIA IN DEVELOPING BRAIN INDIRECTLY RESPOND TO GABA- AND GLUTAMATERGIC ACTIVITIES BY SENSING THE RESULTING INCREASE IN EXTRACELLULAR POTASSIUM.

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Microglial cells invade the brain during early postnatal development, migrate preferentially along fiber tracts to their final position and transform from the ameboid to a ramified form. Signals by which they communicate with other brain cells are largely unknown at this early developmental stage. In the present study, we studied ameboid microglia in postnatal corpus callosum which accumulated on the surface of acute brain slices obtained from 6-8 days old NMRI mice. Whole-cell patch clamp recordings from microglia revealed that both, GABA and glutamate trigger an increase in the inward K^+ conductance. When microglial cells were removed from the slice surface, the effect of GABA and glutamate was abolished indicating that microglia do not respond directly to GABA and glutamate. A likely candidate for the direct signal to microglia is $[K^+]_0$ since an increase in $[K^+]_0$ mimics the response to GABA and glutamate and extracellular K^+ measurements indicating that both transmitters trigger such an increase. While increased $[K^+]_0$ has no effect on microglial chemotaxis and proliferation,

basal release of macrophage inflammatory protein-1 alpha (MIP-1apha, also termedCCL3) was enhanced in situ and in primary microglial cultures. Our results indicate that invading microglia in early postnatal brain can sense GABAergic and glutamatergic signaling indirectly via sensing changes in $[K^+]_0$.

17 ROLE OF EXTRACELLULAR MATRIX IN SENSORY MECHANO-TRANSDUCTION

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Genetic screens carried out in both Caenorhabditis elegans (C. elegans) and Drosophila Melanogaster have suggested that extracellular proteins might be essential for the transducton of body touch and fly bristle movement respectively (Chung et al. 2001. Neuron 29: 415-28; Du et al. 1996. Neuron 16: 183-94; Ernstrom & Chalfie. 2002. Annu Rev Genet 36: 411-53). There is no direct evidence that extracellular factors are crucial for the gating of somatic mechanotransduction channels in vertebrates. In order to investigate this, we have established co-cultures of sensory neurons and skin-derived keratinocytes or fibroblasts. We have asked whether different extracellular environments modify the transduction of mechanical stimuli by DRG neurons. In this project, we have found the molecular nature of the extracellular environment can profoundly modulate mechanosensitive channels in DRG neurons. Matrix derived from keratinocytes has profoundly inhibitory effect on mechanosensitive RA currents. It has been shown Laminin5 is exclusively expressed in Keratinocytes. We found Laminin5 containing matrix can reproduce the inhibitory properties of keratinocytes matrix on DRG mechanosensitivity. Future experiments with laminin5 deficient matrix will allow us to determine if Lamnin5 itself is inhibitory.

18 MODULATION OF NEURONAL MEMBRANE PROPERTIES BY THE COXSACKIEVIRUS-ADENOVIRUS RECEPTOR

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The coxackie virus and adenovirus receptor (CAR) was originally identified as a cell surface protein enabling both viruses to interact with cells. Besides this pathological role as a virus receptor, the physiological function in the CNS is largely unknown. CAR is a member of the Ig superfamily composed of two Ig-like domains, a transmembrane stretch and a cytoplasmic segment. CAR is expressed early in development on neurons and becomes restricted to synapse-rich layers at more advanced stages. Application of the fiber knob of the adenovirus, which binds to CAR, resulted in longer neurites in comparison to the untreated cell cultures. Furthermore, the formation of cell aggregates was reduced by the fiber knob. By using whole-cell patch clamp technique we analyzed the effect of the fiber knob on passive membrane properties and synaptic activity. The fiber knob was able to reduce the membrane resistance (R_m). Consistently, in CAR deficient neurons R_m was significantly higher compared to wild type neurons, and application of fiber knob had no effect on R_m on CAR-deficient neurons. Thus, CAR may influence R_m via membrane proteins with a membrane conductance. Gap junction proteins form large pores with a high permeability and might therefore be candidate proteins regulated by CAR and the fiber knob. In line with this hypothesis, application of different connexin blockers results in a significant increase in R_m in wild type but not in CAR deficient neurons. As a consequence of the absence of CAR, which seems to be essential for the regular development, synaptic connectivity was diminished, as shown by reduced frequency of inhibitory postsynaptic currents. Our results suggest that CAR might influence membrane resistance by modulating the function of gap junctions. As a consequence for impaired electrical coupling in the CAR deficient neurons, formation of synaptic circuits is reduced.

19 PRG-5 IN CULTURED NEURONS INDUCTS DENDRITIC-SPINE FORMATION

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Dendritic spines are small protrusions off the dendrite that receive excitatory synaptic input. In the developing brain, spines show highly dynamic behaviour thought to facilitate the formation of new synaptic contacts. Here, we report that the six transmembrane protein plasticity related gene 5 (PRG-5), a new member of the PRG family, which defined a novel sub-class of the LPP super family, induces dramatic morphological rearrangement in HEK cells and promotes the formation of spines in cultured neurons from mouse brain. PRG-5 is high expressed in the brain and shows a specific expression pattern during brain development where PRG-5 expression is already detected at embryonic day 14. PRG-5 contains three domains on the extra cellular loops, named C1, C2 and C3 with high sequence homologies to the amino acids residues of the LPP family members. The three domains in LPP members are responsible of the ectophosphatase activity. Mutagenesis experiments

in PRG-5 have shown a possible role for residues within the domain C2 and C3, that are crucial for induction of spines. These observations suggest that PRG-5 may be a novel integral membrane protein involved in regulating dendritic-spine morphology by a "catalytic domain" detected in both C2 and C3 protein domains.
This study is supported by the DFG (BR 2345/11-1) and NäFog-stipendium for P. Coiro

20 DEVELOPMENTALLY REGULATED EXPRESSION, LOCALIZATION AND FUNCTIONAL REGULATION OF CALEB, AN EGF-LIKE PROTEIN

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The establishment of precise and selective synaptic connections between neurons during embryonic and early postnatal development depends on the coordinated interplay of an orchestra of molecular components. One these components is CALEB (**c**hicken **a**cidic **l**eucine-rich **E**GF-like domain containing **b**rain protein), a transmembrane protein. Due to its structural features, it belongs to the EGF-family. It was shown that CALEB is converted by neuronal activity and involved in regulating neuronal connectivity early in development. Analysis of the expression of CALEB by immunohistochemistry, immunoblot and RT-PCR showed that it is restricted to the central nervous system. It appeared in embryonic and early neonatal stages in development and expression peaks between postnatal day 10 and 20, a period of synaptogenesis and synapse refinement. Subcellular localization of CALEB studied by bio- and immunocytochemical methods in dissociated neuronal cell cultures revealed that CALEB is predominantly located in plasma membranes of dendrites and cell bodies, but not in axons. Double immunostaining of CALEB together with pre- or postsynaptic proteins provided evidence for a partial localization on synapses. Protein phosphorylation and dephosphorylation are pivotal steps in signal transduction and play a key role in the regulation of many cellular processes. Therefore, potential Phosphorylation sites of CALEB were analyzed by mass spectroscopy. In summary, the developmentally regulated expression pattern and localization of CALEB supported our physiological studies and suggests that CALEB is implicated in the formation of neuronal circuits.

21 COMPLEMENTARY CONTRIBUTIONS OF PREFRONTAL NEURON CLASSES IN ABSTRACT NUMERICAL CATEGORIZATION

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A variety of neuronal classes build the basis of the cortex, but their contributions to cathegorical knowledge has remained unclear. We found that extracellular recorded waveforms from macaque prefrontal cortex can be separated into two subpopulations. One subpopulation is characterized by narrow spike waveforms and shares many features with inhibitory interneurons whereas the features of the other subpopulation resemble those of pyramidal cells. In a cognitively demanding numerosity discimination task, the neuron classes followed different encoding schemes. Whereas the putative interneurons were recruited with a high reliability of stimulus discrimination but with low stimulus selectivity, the putative pyramidal cells encoded numerical values highly specifically. These findings argue for a devision of labor between neuron classes in a feedforward design in which interneurons contribute highly reliable information across a broad range of stimuli whereas pyramidal cells could represent a more definite stimulus representation one step further in the decision process.

22 ALPHA-1A ADRENERGIC RECEPTORS REGULATE NEUROGENESIS AND COGNITIVE FUNCTION

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Neurogenesis has potential as a treatment for epilepsy and neurodegeneration. The endogenous neurotransmitter norepinephrine (NE) may be involved in promoting neurogenesis through the activation of alpha-1A adrenergic receptors (α_{1A}-ARs). However, our understanding of the α_{1A}-AR function has been limited due to a lack of specific ligands and antibodies. To address this, transgenic mice were generated which over-express the α_{1A}-AR with enhanced green fluorescent protein (EGFP) or constitutively active mutant (CAM) α_{1A}-ARs. Knockout (KO) α_{1A} mice were also generated. Immunohistochemistry showed that CAM α_{1A}-AR mice had increased BrdU incorporation in vivo in the subventricular zone (SVZ) compared to normal. CAM α_{1A} and α_{1A}-AR-EGFP had increased numbers of hippocampal interneurons compared to normal and KO α_{1A}-AR. Increased numbers of interneurons may affect certain cognitive processes such as learning

and memory as well as seizure susceptibility. To assess cognitive function, normal, α_{1A}-AR-EGFP, CAM α_{1A}, and KO α_{1A}-AR mice were tested using the multi-component T-, Morris water and Barnes mazes. CAM α_{1A} and α_{1A}-AR-EGFP mice displayed enhanced cognitive abilities compared to normal mice. In all mazes, KO α_{1A}-AR mice displayed the worst cognitive function. Treating normal mice with the selective α_{1A}-AR agonist cirazoline also showed enhanced learning and memory processes. Furthermore, when treated with the epileptogenic agent flurothyl, CAM α_{1A} and α_{1A}-AR-EGFP mice showed an increase in latency periods preceding seizures compared to normal mice. These results suggest that stimulation of α_{1A}-ARs may offer a new therapeutic strategy for increasing cognitive function and treating neurodegenerative diseases. Supported by ND EPSCoR EPS-0447679, NSF CAREER 0347259, and NIH COBRE P20RR017699.

23 'NORMAL' AND 'INVERSE' NEUROVASCULAR COUPLING AND SUPPRESSION OF LOW-FREQUENCY VASCULAR FLUCTUATIONS DURING CORTICAL SPREADING DEPOLARISATION IN THE HUMAN BRAIN

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The term 'default mode' describes the process that the brain remains active in an organised fashion during rest. Low-frequency fluctuations of regional cerebral blood flow (rCBF) reflect neurovascular coupling in the 'default mode'. Cortical spreading depolarisations (CSD) suppress the resting electrocorticographic activity and, thus, disrupt the 'default mode'. Neurovascular coupling during CSD is either characterised by transient hyperperfusion under normal conditions or is 'inverse' and characterised by marked hypoperfusion in tissue at risk of progressive damage. Here, we performed a prospective study assessing neurovascular coupling during CSD in ten patients with stroke or traumatic brain injury. Simultaneous recordings of rCBF with laser-Doppler flowmetry and the electrocorticogram using subdural opto-/electrode strips revealed that CSD shows the full spectrum from 'normal' to 'inverse' neurovascular coupling and attenuation of low-frequency vascular fluctuations in the human brain. The option for a novel 'functional marker' of progressive ischaemic brain damage is suggested observable by vascular imaging techniques. 'Inverse' coupling is suggested as a novel target for treatment development.

24 GLYCINERGIC TONIC INHIBITION OF HIPPOCAMPAL NEURONS WITH DEPOLARISING GABAERGIC TRANSMISSION ELICITS HISTOPATHOLOGICAL SIGNS OF TEMPORAL LOBE EPILEPSY

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An increasing number of epilepsy patients are afflicted with drug-resistant temporal lobe epilepsy (TLE) and require alternative therapeutic approaches. High-affinity glycine receptors (haGlyRs) are functionally adapted to tonic inhibition due to their response to hippocampal ambient glycine, and their synthesis is activity-dependent. Therefore, in our study, we scanned TLE hippocampectomies for expression of haGlyRs and characterised the effects mediated by these receptors using primary hippocampal neurons. Increased haGlyR expression occurred in TLE hippocampi obtained from patients with a severe course of disease. Furthermore, in TLE patients, haGlyR and KCC2 expressions were inversely regulated. To examine this potential causal relationship with respect to TLE histopathology, we established a hippocampal cell culture system utilising tonic inhibition mediated by haGlyRs in response to hippocampal ambient glycine and in the context of a high Cl- equilibrium potential, as is the case in TLE hippocampal neurons. We showed that hypoactive neurons increase their ratio between glutamatergic and GABAergic synapses, reduce their dendrite length and finally undergo excitotoxicity. Pharmacological dissection of the underlying processes revealed ionotropic glutamate and TrkB receptors as critical mediators between neuronal hypoactivity and the emergence of these TLE-characteristic histopathological signs. Moreover, our results indicate a beneficial role for KCC2, since decreasing the Cl- equilibrium potential by KCC2 expression also rescued hypoactive hippocampal neurons. Thus, our data support a causal relationship between increased haGlyR expression and the emergence of histopathological TLE-characteristic signs, and they establish a pathophysiological role for neuronal hypoactivity in the context of a high Cl- equilibrium potential.

25 COMPLEMENT C1Q IS A PROINFLAMMATORY STIMULUS, AND MANNOSE-BINDING LECTIN IS AN ANTI-INFLAMMATORY STIMULUS, FOR MICROGLIAL ACTIVATION

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Microglia, the immune resident cells of the central nervous system, permanently screen brain tissue and respond to any kind of pathology and damage. This response is strongly correlated with changes in a broad range of microglial functions like transformation of cell morphology, enhanced release of cytokines, chemokines or nitric oxide and the presentation of antigens. In our study, we have analysed the effects on microglial properties of key components and potential initiators of the classical and lectin complement cascade, C1q (Complement factor 1q) and MBL (Mannose binding lectin). We show that C1q, the first component of the classical complement cascade system, can trigger the release of IL6, TNF-alpha, and nitric oxide and the oxidative burst in rat primary microglial cells similar to the classical pro-inflammatory stimulation by LPS. By contrast, MBL, the first component of the lectin pathway of complement failed to trigger these parameters, but attenuated the pro-inflammatory response parameters of LPS. C1q also triggers an intracellular Ca^{2+} increase. These findings indicate that C1q fosters while MBL attenuates microglial activation.

26 PROTEASOME ACTIVITY RESTRICTS LONG-TERM MEMORY FORMATION IN HONEYBEES (APIS MELLIFERA)

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Proteasomes are multi-protein complexes that are degrading proteins. Their target proteins are tagged with ubiquitin by a ubiquitin ligase before degradation, to be recognized by the proteasomes. The ubiquitin-proteasome system plays a crucial role in a number of neuronal processes including axon guidance, synaptic development, synaptic function and synaptic plasticity. Moreover, a role of the ubiqitin-proteasome in long-term memory formation has been demonstrated. But these results are contradictory. In the crab *Chasmagnathus* the ubiquitin-proteasome system is necessary for the formation of long-term memory, whereas activity of the ubiquitin-proteasome system in the amygdala of rats restricts formation of a long-term memory in a fear conditioning paradigm. In this study we examine the role of the ubiquitin-proteasome system in the honeybee (Apis mellifera), an invertebrate model system for learning and memory. We here examined an appetitive pavlovian learning paradigm, the olfactory conditioning of the proboscis extension response (PER). We systemically injected two proteasome inhibitors at different time points before and after acquisition and test their effects on learning and memory formation. We find that only a long-term memory is affected by the application of these inhibitors after acquisition, whereas acquisition itself and middle-term memory remain unaffected regardless when the inhibitors were applied. Our results support data from the rat showing that the ubiquitin-proteasome system restricts long-term memory formation. Thus it appears that the ubiquitin-proteasome system is important to prevent inadequate long-term memory formation.

27 CORTICAL CAPILLARIES POSSESS ACTIVE CONTRACTILE ABILITIES IN SLICE AND IN VIVO: A TWO-PHOTON STUDY

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The role of capillaries in the regulation of cerebral blood flow remains largely unexplored— yet pericytes, the second cell type of CNS capillaries besides endothelial cells, are known possess contractile properties *in vitro* in retinal and cerebellar preparations (Peppiatt et al., Nature 443:700-704, 2006). The study of vasoactivity in brain capillaries *in vivo* has been hampered by the difficulty to directly observe them. We have used the β-actin-eGFP transgenic mouse in conjunction with two-photon microscopy to overcome this obstacle. In these mice, the expression of GFP by endothelial cells and pericytes allows the imaging of dynamic changes of capillary morphology at high resolution. In slices of the sensory cortex, we have observed a significant constriction occurring in nearby capillaries after local application of the thromboxan-A2 receptor agonist U46619. The constriction was concentration-dependent, and prevented by the thromboxan-A2 receptor antagonist, SQ 29,548. Morphologically, the constriction mostly showed a sphincter-like pattern and was located near pericytes. *In vivo*, capillaries showed localized reductions of capillary diameters, mimicking the morphological features observed in the slice. Overall, a moderate decrease of

capillary diameters was noted *in vivo*, paralleled by reductions of capillary red blood cell velocity and perfusion. Our results suggest that capillaries can act as putative regulators of cortical cerebral blood flow, which opens new avenues for our understanding of cerebral blood flow regulation in the normal and diseased brain.
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28 HETEROSYNAPTIC PLASTICITY AT THE HIPPOCAMPAL OUTPUT

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The direct cortical input (dCI) to the hippocampus comprises axonal projections from the entorhinal cortex that bypass the dentate gyrus and directly innervate CA3, CA1 and the subiculum. This input has major importance for memory formation as it provides positional information to hippocampal place cells (Brun et al., 2008). The subiculum (SUB) is regarded as the principal output area for the hippocampus and was shown to play a critical role in memory formation, however, mechanisms of synaptic plasticity at dCI-SUB synapses remain unknown. Here we report that both homosynaptic long-term potentiation (LTP) and long-term depression (LTD) at dCI-SUB synapses affect synaptic strength of the CA1-SUB input and that GABAergic transmission controls the direction of this heterosynaptic plasticity. In acute brain slices of juvenile Wistar rats, EPSPs of single subicular neurons were recorded with sharp microelectrodes upon stimulation of dCI/CA1 efferents. Standard high- (100 Hz) and low-frequency (1 Hz) protocols were applied to induce LTP and LTD, respectively. High-frequency stimulation of dCI-SUB efferents induced LTP at both dCI and CA1 inputs, whereas induction of LTP at CA1-SUB efferents was input-specific. Blocking GABAergic transmission with bicuculline converted the heterosynaptic LTP to LTD. Similarly, low-frequency stimulation of dCI-SUB synapses induced LTD of the dCI input and a heterosynaptic LTP at CA1-SUB synapses, which could be switched to heterosynaptic LTD by bicuculline. No heterosynaptic effects were observed after induction of LTD at CA1-SUB synapses. In this study we demonstrate for the first time that synaptic plasticity can be induced at dCI-SUB synapses. The heterosynaptic effects suggest that the dCI has modulatory influence on the hippocampal output, and that this modulation is mediated by inhibitory networks. Further experiments are necessary to uncover which receptors are involved in both homosynaptic and heterosynaptic plasticity of the dCI-SUB input.

29 INVESTIGATION OF SIGNALLING PATHWAYS NECESSARY FOR CALEB/NGC- DRIVEN DENDRITIC SPINE COMPLEXITY

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Dendritic spines, specialized actin-based protrusions emerging from dendritic shafts, are the primary sites of excitatory synapse formation and are thought to function as the basic unit of synaptic integration. Transmembrane proteins are important for connecting extrinsic cues, which regulate dendrite and spine formation, to intracellular mediators of cytoskeletal rearrangement. Recently we showed that the transmembrane protein CALEB/NGC (Chicken Acidic Leucine-rich EGF-like domain-containing Brain protein/Neuroglycan C), a neural member of the EGF family, mediates dendritic tree and spine complexity but that the signalling pathways in the respective processes differ. We found that the extracellular EGF-like domain of CALEB/NGC is necessary and sufficient for both, increasing dendritic branching and stimulating spine formation. However, in contrast to CALEB/NGC-mediated dendritic branching, CALEB/NGC-induced spine formation is not dependent on an active phosphatidylinositide 3-kinase (PI3K)-Akt-mammalian target of rapamycin (mTOR) signalling pathway. Up to now, investigations of the proteins known to interact with CALEB/NGC have not shed light on this divergence. For a more detailed characterization of these signalling pathways we performed a yeast-two hybrid screen and identified B56ß, a subunit of PP2A, to interact with CALEB/NGC. B56b was found to inhibit dendritic branching but did not interfere with the intracellular signalling mechanisms of CALEB/NGC-mediated dendritic spine complexity.
Literature:
Brandt et al., 2007 EMBO J 26, 2371-2386
Brandt et al., 2008 FASEB J, accepted

30 NEUROVASCULAR COUPLING AND CEREBRAL METABOLIC RATE OF OXYGEN: EFFECTS OF BRAIN HYPOTHERMIA

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Background: Neuronal activation is accompanied by a local increase in cerebral blood flow (CBF) and

in cerebral metabolic rate of oxygen (CMRO2). From combined measurements of CBF and hemoglobin concentration, relative changes in CMRO2 during functional challenges can be calculated. The quantitative relationship between basal CMRO2 and brain temperature changes over a range of 10K (Q10) has not yet been determined with this method and can serve as a validation. Then again, the influence of hypothermia on neurovascular coupling is not known. We addressed these issues by studying the effects of graded hypothermia in a rat model of neurovascular coupling in the somatosensory cortex.
Methods: Anesthetized Wistar rats underwent surgical preparation of a closed cranial window over the somatosensory cortex. Using Laser Doppler flowmetry and optical spectroscopy, changes in CBF and in hemoglobin concentration were measured continously. Furthermore, an electroencephalogram (EEG) was simultaneously recorded from the measurement site. By the application of ice packs, whole-body hypothermia was generated, followed by re-warming.
Results: Hypothermia led to a decrease of spontaneous CBF and $CMRO_2$. The calculated Q10 value for $CMRO_2$ was 4.4 (95% Confidence Interval: 3.7 – 5.1). Parallel to CBF and $CMRO_2$, the power of the EEG low-frequency-band decreased. Functional changes of CBF and $CMRO_2$ were reduced during hypothermia as well as the amplitudes of somatosensory evoked potentials.
Conclusions: With optical methods, spontaneous changes in relative $CMRO_2$ can be quantified, revealing a Q_{10} for $CMRO_2$ that is well in the range of literature values. During hypothermia, neurovascular coupling is preserved. This applies to CBF changes accompanying spontaneous ongoing activity as well as CBF changes during functional activation.
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31 ROLE OF THE TSH1 GENE IN OLFACTORY BULB – DEVELOPMENT

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The early development of the olfactory bulb is still poorly understood. We chose to analyse the function of the Tsh1 gene, which we had shown to be expressed in cells of the outer granule cell layer of the embryonic olfactory bulb. Our aim was to determine the function of Tsh1, a potential integrator of signaling downstream of cell surface receptors (e.g. Wnt/beta-catenin signaling) and a partner for Hox-family transcription factors in olfactory bulb development. The methods employed were classical mutagenesis in the mouse, together with immunohistochemistry, in situ hybridisation and microarray analysis. Tsh1 was expressed in an early emigrating population of GABA-ergic interneurons, generated in the rostral telencephalon around E11-E12. In Tsh1 homozygous null embryos, mutant cells clumped together and failed to distribute radially within the olfactory bulb, a phenotype associated with changes in Semaphorin signaling. In addition, the Tsh1 mutant cells failed to activate expression of GABA-ergic markers such as GAD67 and GABA.
Conclusions: Tsh1 is essential for the correct radial migration and differentiation of a pioneer population of GABA-ergic granule cell neurons within the olfactory bulb. Tsh1 mutant cells failed to express Semaphorin 3c and a signaling mediator cypin, which may account for the aberrant clumping of mutant cells within the center of the olfactory bulb.

32 EXPRESSION ANALYSIS OF THE PLASTICITY RELATED GENE-1

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PRG-1 is a membrane associated protein specifically expressed in neurons. It is only expressed during late developmental stages and might be involved in the LPA signal transduction pathway. PRG-1 plays also an important role in axonal outgrowth and cortical layer formation. The interesting temporal and spatial expression pattern of PRG-1 raises the question of it´s specific regulation. In silico analysis indicates a GC-rich TATA-Box less promoter sequence. Several transcription start points of the murine gene were mapped via 5´-RACE. Prior treatment with tobacco acid pyrophosphatase strongly favoured the detection of CAPed full length transcripts. In order to analyze *in vivo* expression pattern of PRG-1, we generated a mouse model using the BAC (bacterial artificial chromosome) transgenic technology according to N. Heintz (Rockefeller Institute). In this transgenic mouse line the reporter protein EYFP is expressed in the same way as the endogenous PRG-1, controlled via *in situ* hybridisation and immunhistochemical stainings. The strict neuronal expression of the reporter gene in absence of conserved motivs mediating this expression pattern, like e.g. REST raises hope to identify a new regulatory motiv, which must be localised on the 200 kb sequence of the inserted BAC. Besides expression analysis this reporter-mouse-model allows the analysis of PRG-1 regulation during development and in cultured organotypic slice preparations .

33 MACROPHAGE/MICROGLIA ACTIVATION AND ENGRAFTMENT DURING PERSISTENT BORRELIAL CNS INFECTION

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Relapsing fever (RF) is a multisystemic borrelial infection with frequent neurologic involvement referred to as neuroborreliosis. RF is characterized by peaks of spirochetemia, attributable to antibody selection against variable serotypes. In the absence of B cells, serotypes cannot be cleared, resulting in persistent infection. We previously identified differences in spirochetemia and disease severity during persistent infection of SCID mice with isogenic serotypes 1 (Bt1) or 2 (Bt2) of of the RF spirochete *Borrelia (B.) turicatae*. To study the consequences of persistent CNS-infection with *B. turicatae*, B cell (Igh6-/-) and B and T (Rag1-/-) cell-deficient mice were inoculated with Bt1 or Bt2. Bt1 was more tissue tropic than Bt2, not only for brain but also for heart. Igh6-/- mice developed more severe clinical disease than Rag1-/- mice. Bt1-infected brains had widespread microgliosis/brain macrophage activation despite localization of spirochetes in the leptomeninges rather than the brain parenchyma. Persistent infection did not result in injury to the brain parenchyma. Using oligoarray analysis we found that the majority of 116 significantly upregulated genes in the brain of infected Igh6-/- mice refer to functions of the immune response. 27% are known to be upregulated in activated macrophages/microglia. CXCL13 was the most upregulated gene in the brain. In the blood, CXCL13 and IL-10 were the most abundant chomokines/cytokines. Pathogen load positively correlated with IL-10 in blood, brain, and heart. IL-10 injected systemically reduced disease, spirochetemia, CXCL13 production as well as microgliosis. In the brain, activated microglia were the main source of IL-10. To investigate the influence of persistent borrelial infection on engraftment and differentiation of migratory myeloid cells in the brain, we presently use transplantation of GFP marked BM cells into SCID and immunocompetent mice. We observe widespread intraparenchymal engraftment of F4/80+/Iba-1+/gfp+ cells, predominantly in the proximity of meningeal inflammation and with several morphologically distinct forms of macrophages/microglia. CNS involvement in B cell-deficient mice persistently infected with *B. turicatae* is characterized by prominent microgliosis as well as upregulation of genes suggesting a vigorous immune response without detectable injury. Systemic and microglial production of IL-10 may play a protective role as a downregulator of inflammation and pathogen load. Present studies focus on myeloid cell engraftment and the origin of IL-10 secreting macrophages/microglia during persistent borrelial CNS-infection.

34 COGNITIVE CONTOL OF GOAL-DIRECTED BEHAVIOR: EVENT-RELATED POTENTIALS ASSOCIATED WITH SELF-GENERATED AND EXTERNALLY INDUCED FAILURE

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Goal-directed behavior requires not only the continuous monitoring of failures but also the causal attribution of these failures in order to adjust behavior appropriately. It has been suggested that the error-related negativity (ERN) following response errors and the feedback-related negativity (FRN) following negative response feedback reflect functionally related components of the event-related brain potential (ERP) in performance monitoring. However, the majority of studies focused only on unfavorable outcomes which are associated with self-generated errors in reaction time tasks. The objective of the present research was to examine whether the performance monitoring system is also activated by externally caused failure. Participants performed a choice reaction time task in which technical problems with the response device were simulated leading to false negative feedback. As expected, an ERN was observed following self-generated errors, and a FRN was elicited following technical malfunctions. Based on the assumption of a common neural generator for both ERP components, theses findings suggest a more general role of the performance monitoring system in signaling the need for adjustment, whenever the outcome of an action is worse than intended, independently of whether the failure to achieve an action goal is due to internal or external factors.

35 APOLIPOPROTEIN E DEFICIENCY ENHANCES TAU HYPERPHOSPHORYLATION IN P301L MUTANT HUMAN TAU MICE

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Clinical studies suggest a link between Alzheimer´s disease (AD) and imbalances in cholesterol metabolism and a further modification by the apolipoprotein E (apoE) genetic polymorphism, a risk factor for AD. But whether that link between serum cholesterol and AD is due to an influence of brain cholesterol homeostasis is yet not understood. Cerebral cholesterol imbalances may trigger the amyloid toxic cascade or influence tau phosphorylation and tangle formation rather independently. ApoE plays an important role in the

cholesterol homeostasis of neurons. To investigate the possible link between cholesterol and tau pathology under the influence of apoE, we used double transgenic mice expressing P301L mutant human tau but deficient in apoE (TauAPOE-/-) and P301L tau APOE wild type mice (TauAPOE+/+). These mice express the longest human four-repeat tau isoform with the human pathogenic mutation P301L and show age-dependent cytoskeletal changes which resemble those found in AD brain. Mice were kept on a cholesterol-enriched diet (1% cholesterol) or a control diet. Changes in tau phosphorylation and conformation were most pronounced in the apoE-deficient mice but seemed to be attenuated by the cholesterol-enriched diet. TauAPOE+/+ mice showed remarkably less AT8-(phosphorylation-dependent tau antibody) and MC1-immunoreactivity (conformation-dependent) than the TauAPOE-/- mice and an opposite diet effect. Total brain cholesterol was higher in the TauAPOE-/- mice. On the cholesterol-enriched diet, TauAPOE+/+ mice showed an increase in total brain cholesterol while the apoE-deficient mice had no further increase although the serum cholesterol level was further increased by the diet in these animals. There was no clear correlation between total brain cholesterol and tau pathology independent of APOE genotype. The apoE deficiency seemed to influence the pathological tau processing in P301Ltau mutant human tau mice more than the high serum cholesterol levels induced by diet.

36 TRPV1, A SYNAPTIC PROTEIN

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Electrophysiological studies demonstrate TRPV1 to be involved in neuronal signal transmissions. Its localization along nociceptor fibres is proven but evidence demonstrating the presence of TRPV1 in synaptic structures is lacking. We now find TRPV1 in DRG neuron derived F11 cells at filopodial tips and cell-cell contact regions. There it co-localizes with pre- and post-synaptic proteins such as bassoon, PSD95, and PSD-Zip45. Additionally, it is present in cytoplasmic transport packets, which deliver pre-assembled synaptic structures. We observed them in life cells to perform characteristic fast saltatory movements. Also, when expressed in cultured cortical neurons, TRPV1 localizes to spines. Accordingly, spine morphology is strongly altered upon TRPV1 activation. In filopodia and neurite like structures of F-11 cells TRPV1 also co-localizes with synaptic vesicular proteins such as clathrin, snapin, and synapsin. In F11 cells vesicle turnover can be visualized by uptake of the fluorescent dye FM-464. Vesicle release is strongly induced by activation of TRPV1 with the endogenous agonist NADA. We conclude that TRPV1 can act both as pre- as well as post-synaptic protein. It is present in cycling vesicles at active zones. Activation of TRPV1 modulates the morphology as well as the function of synaptic structures.

37 EFFECTS OF SALICYLATE APPLICATION ON THE SPONTANEOUS ACTIVITY IN BRAIN SLICES OF THE MOUSE COCHLEAR NUCLEUS, MEDIAL GENICULATE BODY AND PRIMARY AUDITORY CORTEX

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Salicylate is a well - known substance to produce reversible tinnitus in animals and humans as well. It has been shown that systemic application of salicylate changes the neuronal spontaneous activity in several parts of the auditory pathway. The effects observed in central auditory structures in vivo could be based on the changed afferent cochlear input to the central auditory system or in addition by a direct effect of salicylate onto neurons within the auditory pathway. An immediate influence of local salicylate application on spontaneous activity of central auditory neurons has already been described for the inferior colliculus (IC) in brain slice preparations. As spontaneous activity within all key structures of the central auditory pathway could play an important role in tinnitus generation, the present study investigated direct effects of salicylate superfusion on the spontaneous activity of the deafferentiated cochlear nucleus (CN), medial geniculate body (MGB), and auditory cortex (AC) in brain slices. Out of 72 neurons, 73.4 % responded statistically significantly to the superfusate by changing their firing rates. 48.4 % of them increased and 51.6 % decreased their firing rates, respectively. The mean change of firing rate upon salicylate superfusion was 24.4 %. All responses were not significantly different between the brain areas. The amount of neurons which responded to salicylate and the mean change of firing rate was much higher in the IC than in the CN, MGB and AC. This contributes to the hypothesis that salicylate-induced tinnitus is a phantom auditory perception mainly related to hyperexcitability of IC neurons. However, the present results suggest that the individual, specific salicylate sensitivity of CN, MGB and AC neurons can modulate the salicylate-induced generation of tinnitus.

38 ACUTE AND LONG-TERM EFFECTS OF NOISE EXPOSURE ON THE ASCENDING AUDITORY PATHWAY EVALUATED WITH MANGANESE-ENHANCED MAGNETIC RESONANCE IMAGING (MEMRI)

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Noise exposure leads beside cochlear hair cell loss to profound long term changes within the central auditory pathway. A modified spontaneous activity, changes in cell density and neurotransmitter action were reported for several auditory structures. It is not possible yet to distinguish between the changes based on the reduced input from the noise-damaged organ of corti and neuronal changes directly related to the auditory overstimulation. For the understanding of noise induced functional disabilities, it seems to be important to clarify the influence of these two mechanisms. While hair cell loss appears slowly in the early days after treatment, it should be possible to study effects on central auditory structures at different stages after an overstimulation. In this study, normal hearing mice were noise-exposed (3h, 115 dB SPL, white band noise 5-20 kHz) under anaesthesia. At the end of the treatment or one week later animals received an i.p. injection of manganese chloride to monitor neuronal activity by using 7T-MRI scanning (replacement of calcium influx by manganese). Signal intensities of dorsal (DCN) and ventral (VCN) cochlear nucleus, periolivary nucleus (PON), inferior colliculus (IC), medial geniculate body (MGB) and primary auditory cortex (AI) were measured and compared with controls. The acute group with temporary hearing loss showed a significant signal enhancement in the DCN and VCN. The animals characterized by a permanent hearing loss have a significantly higher neuronal activity also in higher structures of the auditory pathway. The results demonstrate that acoustic overstimulation directly influences the neuronal network within the central auditory pathway. Acute noise exposure seems to affect the lower auditory pathway, whereas long-term effects could also be observed in higher structures.

39 ALTERATIONS IN THE ENTORHNAL CORTEX NETWORK OSCILLATIONS IN A MOUSE MODEL OF MESIAL TEMPORAL LOBE EPILEPSY

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Mesial temporal lobe epilepsy (mTLE) is the most common form of epilepsy, characterized by recurrent complex partial seizures and hippocampal sclerosis. mTLE patients often display shrinkage of the entorhinal cortex (EC), which has been attributed to neuronal loss in medial EC (mEC). Since the EC occupies a pivotal position in gating hippocampal input and output the dysfunction of this region may contribute to epileptogenesis in humans. To identify the anatomical and functional changes, we performed field potentail and patch-clamp recordings in the EC in a kainite (KA) model of mTLE 3-4 weeks following intrahippocampal KA-injection. Field potential recordings were done from different region of the EC. Whole-cell patch-clamp recordings in current and voltage clamp mode were obtained from mEC layer III parvalbumin positive (PV+) interneurons from control and KA-treated mice. Our results show that KA-induced field gamma oscillatory activity in the EC has significantly higher power in epileptic than in control mice. Morphological analysis of PV+ interneurons in layer III of the EC revealed no clear differences in the axonal arborisation pattern between control and experimental groups. As cell loss in layer III of the EC is restricted to excitatory cells we presume a stronger interaction between the GABAergic interneurons in mTLE. An altered interaction between the GABAergic inhibitory interneurons in the EC network may contribute to altered rhythmogenesis and the development of seizure activity in mTLE.

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40 FREQUENCY AND PHENOTYPE OF NK CELLS IN MULTIPLE SCLEROSIS

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Multiple Sclerosis (MS) is considered an autoimmune disease of the central nervous system of unknown pathogenesis. We previously demonstrated a significantly lower expression of the chemokine receptor CX3CR1 on NK cells in relapsing-remitting (RR) MS patients compared to healthy individuals and found an association between disease activity and frequency of CX3CR1-positive NK cells in MS patients. To better elucidate the possible role of NK cells (and in particular CX3CR1-expressing NK cells) during MS pathology, we investigated the frequency of NK cells in cerebrospinal fluid (CSF) of MS patients, and the phenotype and effector function of CX3CR1+ vs. CX3CR1- NK cells. The frequency of NK cells in the CSF and blood was compared between MS patients and patients with non-inflammatory neurological diseases (NIND). Our data show the blood/CSF ratio of NK cells is 7:1 in MS patients and is 2:1 in NIND. The ratio of T cells was comparable between the two groups of patient.

Related to the investigation of CX3CR1-expressing NK cells, we demonstrate that human CX3CR1negative/low- NK cells produce increased amounts of the cytokines TNF-alpha, GM-CSF, IL-10, IL-13 and IL-5, are more activated (but less cytotoxic), and show increased proliferative capacity in response to IL-2 when compared with the CX3CR1-positive fraction. Thus, in contrast to the CX3CR1-positive NK cells, the NK cells that are low or negative for the receptor, present a regulatory phenotype characterized by a diminished cytotoxicity and a high production of soluble factors. Altogether, our findings highlight the overall importance of NK cells in MS and the necessity to learn more about their role in MS.

41 DENSITY OF ENKEPHALIN EXPRESSING STRIATAL PROJECTION NEURONS AND ENTOPEDUNCULAR DYNORPHIN IMMUNOREACTIVITY ARE UNALTERED IN A MODEL OF PAROXYSMAL DYSTONIA

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The pathophysiology of hereditary dystonia is still unknown, but it is regarded as a basal ganglia disorder. Recent studies in the dtsz hamster, an animal model of paroxysmal dystonia, demonstrated a reduced density of striatal GABAergic interneurons at an age of maximum severity of dystonia (30-42 days of life) in comparison to non-dystonic controls. The reduced density coincides with a decreased neuronal activity and an altered neuronal pattern in the entopeduncular nucleus (EPN), a basal ganglia output structure, which receives inhibitory input from the striatum via the so-called direct pathway. In the present study, the density of striatal met-enkephalin (ENK) expressing GABAergic neurons, which project to the globus pallidus (indirect pathway) and the immunoreactivity of dynorphin A (DYN), which is expressed in striatal neurons of the indirect pathway, were determined in dtsz and control hamsters by using an image analysis system in a blinded fashion to clarify a possible role of an altered ratio between striatal interneurons and projection neurons. Neither the density of striatal ENK^+ neurons nor the immunoreactivity of DYN, determined in the EPN, significantly differed between mutant and control hamsters. Consequently, alterations seem to be restricted to GABAergic interneurons in the dtsz mutant. Thus, the present results support the hypothesis that an altered ratio between striatal interneurons and projection neurons leads to imbalances in the basal ganglia network and results in a reduced neuronal activity and altered pattern in the EPN.

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42 GAMMA OSCILLATIONS AND SPONTANEOUS NETWORK ACTIVITY IN THE HIPPOCAMPUS ARE HIGHLY SENSITIVE TO DECREASES IN PO2 AND CONCOMITANT CHANGES IN MITOCHONDRIAL REDOX STATE

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Gamma oscillations have been implicated in higher cognitive processes and might criticallydepend on proper mitochondrial function. Using electrophysiology, oxygen sensormicroelectrode and imaging techniques, we investigated the interactions of neuronal activity, interstitial pO2 and mitochondrial redox state (NAD(P)H and FAD fluorescence) in the CA3 subfield of organotypic hippocampal slice cultures. We find that gamma oscillations and spontaneous network activity decrease significantly at pO2 levels that do not affect neuronal population responses as elicited by moderate electrical stimuli. Moreover, pO2 and mitochondrial redox states are tightly coupled, and electrical stimuli reveal transient alterations of redox responses when pO2 decreases within the normoxic range. Finally, evoked redox responses are distinct in somatic and synaptic neuronal compartments and show different sensitivity to changes in pO2. We conclude that the threshold of interstitial pO2 for robust CA3 network activities and required mitochondrial function is clearly above the 'critical' value, which causes spreading depression due to generalized energy failure. Our study highlights the importance of a functional understanding of mitochondria and their implications on activities of individual neurons and neuronal networks.

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43 MOLECULAR INTERACTIONS BETWEEN STOMATIN-LIKE PROTEINS AND ACID-SENSING ION CHANNELS

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Stomatin-like proteins (SLPs) are widely expressed across species and tissues. However, the function of this family of membrane-associated proteins remains to be elucidated. Some SLPs bind cholesterol as well as actin filaments and are therefore considered to have a scaffolding function, assembling protein complexes at the plasma membrane. Moreover,

there is evidence of SLPs directly interacting with ion channels. In the nematode worm C.elegans, the stomatin homolog MEC-2 plays an essential role in mechanosensation by anchoring the transduction channel MEC-4 to the cytoskeleton. We are interested in defining the nature of the interactions between mammalian counterparts of the C.Elegans proteins, which have been implicated in mechanotransduction as well. To this end, we have performed co-immunoprecipitation and FRET experiments to examine interactions between mouse stomatin-like protein 3 (mSLP3) and members of the acid-sensing ion channel (ASIC) family. These are sodium channels that are homologous to the C. elegans MEC-4 channel and comprise short intracellular N- and C-termini, two transmembrane domains and a large extracellular loop.All ASIC subunits (ASIC1a, 1b, 2a, 2b, 3 and 4) and mSLP3 were epitope tagged and transiently transfected into two cell lines (COS-7 and CHO) that are thought to contain no endogenous ASICs. We found that mSLP3 did immunoprecipitate with all ASICs. Interestingly, a splice variant of ASIC3, which misses the C-terminus and the second transmembrane domain, also interacted with mSLP3. This suggests that the interaction site is located more towards the N-terminus of the ASIC channels.

44 CALEB, AN ACTIVITY-REGULATED PROTEIN, IS INVOLVED IN THE ESTABISHMENT OF SYNAPTIC CONNECTIONS IN THE CERE-BELLUM

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Proteins, located at the cell surface and modulated by neuronal activity might be promising candidates to transform sensory information into a specific synaptic function including morphological correlates. CALEB, a member of the EGF-family was characterized to be activity-dependent processed on the cell-surface. Developmental regulated expression patterns, with peak levels in periods of synaptogenesis and synapse refinement makes CALEB a promising candidate to be involved in regulation synaptic connectivity. Analysis of synaptic connectivity in the immature colliculus superior revealed that CALEB regulates the release probability of the neurotransmitter, while the number and morphological characteristics of synapses remained unchanged the absence of CALEB. In the immature cerebellum CALEB is expressed within in the Purkinje cell layer, while later in development it is primarily found in the molecular layer. The developmental change in the localization in a period of synapse elimination may suggest a specific function in synapse refinement. Analysis of the climbing fiber - Purkinje cell synapse revealed an earlier maturation of the adult-like, monosynaptic innervation in the CALEB knockout mouse compared to the wild type. This faster synapse elimination appears not to be induced by mGluR-mediated signalling of parallel fibers. However, the GABAergic input to Purkinje cells seems to be reduced, represented by reduced amplitudes of spontaneous inhibitory postsynaptic currents. These changes in the maturation of synaptic connectivity in the cerebellum lead, at least, to deficiencies in the motor coordination of the knockout mouse. In summary, CALEB is an activity-dependent regulated protein, which plays a role in adjustment of neuronal networks.

45 EARLY MATURATION OF GABAERGIC SYNAPSES IN MOUSE RETINAL GANGLION CELLS

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The formation of complex neuronal circuits is coordinated by numerous molecular and cellular mechanisms. To unravel the specific function of proteins that participate in the establishment and modulation of synaptic connections, investigation of transgenic mice remains a promising approach. In order to capitalize fully on these experimental advantages, it is important to establish developmental timelines of the major functional parameters. This study was aimed to characterize the earliest phases of synapse development in mouse retinal ganglion cells (RGCs) by recording spontaneous postsynaptic currents (PSCs). RGCs were identified on the basis of their location in the ganglion cell layer, their soma size and the presence of voltage-activated Na+ currents. First postsynaptic currents were detected at embryonic day 17 with a success rate of about 54.5 % (6/11), while later in development (P6) nearly all RGCs showed synaptic events (96.6 %, 28/29). In the presence of bicuculline, a GABAA receptor blocker, all synaptic currents were completely suppressed, suggesting their GABAergic nature. In the first postnatal week only in three RGCs out of 135 (2.22 %) spontaneous, fast decaying events could be detected, representing most likely glutamatergic currents. By analysing GABA-induced Ca2+ transients we show, that GABA-mediated signalling acts in an excitatory manner in this period. The present results suggest that functional GABAergic synapses with RGCs appear before birth and that GABAergic synaptic transmission precedes that of glutamate in the retina. In this early period GABA acts in a depolarizing manner and takes over an excitatory function.

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46 LYSOPHOSPHATIDIC ACID IN SYNAPSOGENESIS

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Lysophosphatidic acid (LPA) is a small phospholipid with a variety of biological actions. This mediator produces diverse cellular and biochemical responses in a range of different nervous system-derived cells. LPA mediates effects through cell-surface receptors (LPA-1-5), following the intracellular activation of multiple G-proteins. Our real-time PCR analysis of mRNA from hippocampal primary neurons only detected LPA-1, LPA-2 and LPA-4 receptors, whereby LPA-2 receptors exhibited the highest expression. The same results were found *in vivo*. In further experiments we focused on the LPA-2 receptor and analyzed its subcellular localization in hippocampal primary neurons. We located the receptor in the cell body and dendrites. Interestingly, it was colocalized with different pre-synaptic markers and was present in glutamatergic but not in gabaergic neurons. In functional analyses we tested LPA-effects on primary neurons. We discovered a reduction of synaptophysin-positive terminals and a calcium increase after LPA application. LPA-Signaling is controlled *in vivo* by lipid phosphate phosphatases (LPPs), ectoenzymes that regulate LPA-levels through dephosphorylation. In our previous studies we identified a set of proteins that form a novel subclass in the LPP-superfamily, plasticity-related genes (PRGs). Currently we are focusing on PRG-1 alone. Unlike other members of the LPP-family, PRG-1 is specifically expressed in the brain and neurons; presynaptic colocalization has not yet been identified. Immunohistochemistry showed the localization of PRG-1 in filopodia and dendritic spines. Furthermore, an overexpression of PRG-1 was able to attenuate LPA effects in glutamatergic neurons.

47 DRUG TRANSPORTERS IN HUMAN EPILEPTIC BRAIN – FUNCTIONAL STUDIES

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Ectopic expression of multidrug transporter proteins (Pgp, MRP1, MRP2) in astrocytes or neurons has been observed in resected tissue of patients suffering from pharmacoresistant mesial temporal lobe epilepsy. There are also case reports where the application of inhibitors of multidrug transporters improved the outcome of patients. Here we induced pharmacoresistant activity (carbamazepine 50μM or valproate 1mM) in human hippocampal(Hi) and cortical(Co) slices in vitro and we investigated the effect of inhibitors of multidrug transporter proteins by application of probenecid (400μM) and verapamil (40μM). The type of epileptiform activity was rarely affected in the hippocampus (76% stable, 8% replaced by interictal activity, 16% suppressed), in contrast to the cortex (43% stable, 38% replaced, 19% suppressed). The quantitative analysis revealed significant reductions for the combined treatment in slow field potential shift(Hi, Co), maximum amplitude(Hi, Co), frequency of superimposed oscillations(Hi) and duration(Co) of the events. Preliminary analysis of our control experiments showed that a longer incubation time of both inhibitors is more effective in the hippocampus, but not in the cortex. But in the cortex, the inhibitors given alone showed more effect than the application of a single antiepileptic drug. The electrophysiological effects of the inhibitors could not be correlated to the expression rate of multidrug transporter proteins in the hippocampus.

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48 DEVELOPMENTAL DOWN-REGULATION OF EXCITATORY GABAERGIC TRANSMISSION IN NEOCORTICAL LAYER I VIA PRESYNAPTIC ADENOSINE A1 RECEPTORS

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Layer I of the developing cortex contains a dense GABAergic fiber plexus. These fibers provide excitatory inputs to Cajal-Retzius (CR) cells, the early-born neurons in layer I. CR cells possess an extensive axonal projection and form synaptic contacts with excitatory neurons. Interestingly, activity of CR cells declines during the first postnatal week. Here we recorded IPSCs in CR cells at postnatal day (P) 1-2 and P5-7. Blockade of adenosine A1 receptors (A1Rs) increased the amplitude of evoked IPSCs (eIPSCs) and decreased paired-pulse ratio at P5-7 but not at P1-2. A1R activation decreased the mean eIPSC amplitude at P5-7, but failed to affect eIPSCs at P1-2. Ecto-ATPase inhibition completely abolished the A1R-mediated effects suggesting that extracellular ATP is the main source of adenosine. Because A1R blockade did not affect the median mIPSC amplitude, our results demonstrate that adenosine reduces GABA release probability via presynaptic A1Rs at P5-7. As neuronal activity in layer I can depolarize

pyramidal neurons influencing thereby glutamatergic synaptogenesis in the lower cortical layers, postnatal weakening of GABAergic transmission by adenosinergic system might reflect a developmental down-regulation of this excitatory drive when glutamatergic synapses are formed.

49 ACTIVITY OF THE GABA TRANSPORTER 1 REGULATES GABAERGIC SYNAPTIC TRANSMISSION IN STRIATAL PROJECTION NEURONS

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In the present whole-cell patch clamp study we have addressed the possibility that a GABA transporter (GAT-1 or -3) shapes GABAergic synaptic transmission in acute slices of the mouse neostriatum. We have used the degree of GABA(B) receptor activation as a reporting tool to identify alterations of perisynaptic GABA concentration. It was found that presynaptic GABA(B) receptors are functional and inhibit the synaptic release of GABA, and there was no indication of a tonic GABA(B) receptor action under standard conditions. However, treatment with the specific GAT-1 blocker NO-711 resulted in lower amplitudes of evoked IPSCs (eIPSCs), prolonged eIPSC decay and higher paired-pulse ratio (PPR). Subsequent application of CGP55845 (a specific GABA(B)R antagonist) partly restored the eIPSC amplitude and reduced the PPR to control levels. The amplitude of miniature IPSCs decreased after NO-711 treatment independently of GABA(B)R activation. The GAT-3 blocker SNAP-5114 had no significant effect on the eIPSCs, but a contribution of GAT-3 was unmasked by NO-711 suggesting that GAT-1 can compensate for a loss in GAT-3 activity. We conclude that, by mediating the clearance of perisynaptic GABA, GAT-1 controls the degree of presynaptic GABA(B) receptor activation and, therefore, the strength of GABA release. The efficacy of GABA clearance may also affect the GABA(A) receptor-mediated postsynaptic response. Thus, GAT-1 activity should be considered as a factor in the pre- and postsynaptic regulation of GABAergic synaptic transmission in output neurons of the murine striatum.
Supported by a grant of the Deutsche Forschungsgemeinschaft to RG.

50 METABOLIC CONSEQUENCES OF STORE OPERATED CAPACITATIVE CA^{2+} ENTRY

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Metabotropic receptor-mediated Ca^{2+} signals are critical for the crosstalk of neuronal activity and mitochondrial functions. However, very little is known about the effects of store operated capacitative Ca^{2+} entry on the regulation of energy metabolism in neurones. Here we investigated the effects of muscarinic metabotropic receptor activation and subsequent capacitative Ca^{2+} entry on mitochondrial Ca^{2+} concentration ($[Ca^{2+}]m$), mitochondrial membrane potential and oxidative metabolism (NAD(P)H and FAD fluorescence) in hippocampal slice cultures by using electrophysiology (patch clamp recordings and ion sensitive electrodes) and conventional or 2-photon laser scanning confocal microscopy. Application of carbachol (100 μM) transiently increased $[Ca^{2+}]m$, stimulated oxidative metabolism and induced K^+ outward currents. Carbachol-induced responses persisted in Ca^{2+} free solution and blockade of ionotropic glutamatergic and nicotinic receptors as well as voltage-gated Na^+ channels. After carbachol induced depletion of intracellular Ca^{2+} stores in Ca^{2+}-free solution, re-application of 1.6 mM Ca^{2+}-containing solution triggered mitochondrial depolarisation, marked elevations in neuronal $[Ca^{2+}]m$, and extracellular K^+ concentration as well as changes in oxidative metabolism. The metabolic response upon re-application of Ca^{2+} required simultaneous activation of muscarinic receptors as it could be blocked by subsequent application of atropine. By varying the interval between store depletion and Ca^{2+} re-application we determined the time course of the carbachol dependent sensitization of mitochondrial metabolism and $[K^+]o$ transients, which was in agreement with the decay time of the carbachol induced membrane depolarisation in pyramidal cells. Thus we concluded that store-operated capacitative Ca^{2+} entry might regulate energy metabolism in concert with a muscarinic receptor dependent Ca^{2+}-activated K^+ current.
Supported by the Deutsche Forschungsgemeinschaft (SFB 507) to UH and OK.

51 ESTROGEN INDUCES TRPV1-DEPENDENT CYTOSKELETAL REARRANGEMENT

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The non-selective cation channel TRPV1, the cytoskeleton, and the steroid hormone estrogen are known to be involved in nociception. However, little is known if these components are functionally linked. Here we show estrogen to induce rapid morphological changes such as cell retraction, lamellipodia to filopodia transition, varicosity formation and growth cone retraction in DRG-neuron derived F-11 cells expressing TRPV1. The morphological changes in response to estrogen correlate with rapid

rearrangement of the actin network and quick disassembly of dynamic peripheral microtubules in life cells. These effects are dependent on the expression of TRPV1 but cannot be blocked by 5'-I-RTX. 5'-I-RTX is a specific inhibitor of TRPV1 channel opening, thus indicating a channel independent role of TRPV1 in estrogen-induced cytoskeleton rearrangement. Estrogen can act through the classical estrogen receptors, ER-α and ER-β, as well through the recently identified G-protein coupled receptor GPR30. The estrogen derivates G-1 and ICI182,780 are reported to activate specifically GPR30 while not being agonists of the classical estrogen receptors. Estrogen apparently acts through GPR30 on the cytoskeleton as G-1 and ICI182,780 induce similar morphological changes. We conclude that estrogen can act via the novel estrogen receptor GPR30 on TRPV1 expressing neuronal cells by inducing rearrangements of the actin and tubulin cytoskeleton.

52 SEQUENTIAL MATURATION OF SENSORY NEURON MECHANO-TRANSDUCTION DURING EMBRYONIC DEVELOPMENT

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We and others have previously reported the presence of three types of mechanically activated currents in adult mouse dorsal root ganglion (DRG) neurons. These currents can readily be distinguished by their inactivation kinetics and are thus classified into rapidly adapting (RA-type), intermediately adapting (IA-type) and slowly adapting (SA-type) currents. In the present study we asked when during embryonic development sensory neurons acquire these mechanosensitive currents. Our data suggests that mechanosensitive currents emerge in three major waves, which coincide with already well-described epochs in the development of the sensory ganglia. First, at E13.5, mechano-receptors and proprioceptors acquire RA-type currents, followed by nociceptors which start to acquire RA-currents at E15.5. The third wave of mechanosensitivity occurs just after birth when a large proportion of nociceptors acquire SA-type currents. In addition we investigated the electrical properties of developing sensory neurons. We found that both, mechanoreceptors and nociceptors, become electrically excitable immediately after they are born, at E11.5 and at E12.5-E13.5, respectively. Thus the acquisition of electrical excitability precedes that of mechanosensitivity by approximately two days. Moreover, we found that the emergence of mechanically gated currents in nociceptors correlates with significant changes in the electrical excitability of these neurons. Since the first two waves coincide with the innervation of peripheral targets by mechano-receptors (E13.5) and nociceptors (E15.5), we next asked whether target derived factors are required for the acquisition of mechanosensitivity. Therefore DRG neurons from non-mechanosensitive stages were differentiated in-vitro in the presence of different neurotrophins. These experiments strongly suggest that the acquisition of mechanosensitive currents by nociceptors is induced by target derived NGF, whereas the acquisition of RA-currents by mechanoreceptors seems to be a time dependent process which is independent of the presence of neurotrophic factors.
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53 DOES AGING INFLUENCE PHYSIOLOGICAL NEUROVASCULAR COUPLING? A COMBINED DC-AGNETOENCEPHALOGRAPHIC AND TIME-RESOLVED NEAR-INFRARED SPECTROSCOPIC STUDY

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Different fMRI studies have demonstrated that BOLD signal changes are determined by several physiological parameters, such as age. One hypothesis is that age-dependent changes of the cerebral vasculature influence the neuro-vascular coupling, leading to attenuated BOLD responses in spite of similar neuronal activation. To characterize age related dynamics and the interrelation of neuronal and vascular responses, simultaneous unmodulated DC-Magnetoencephalography (DC-MEG, BMSR-2) and time-resolved multichannel near-infrared spectroscopy (trNIRS) were performed in two age cohorts during motor cortex activation. 10 subjects aged 20-25 years compared to 10 subjects aged 70-75 years performed prolonged finger movement periods of the right hand (alternating 30 sec. movement/ 30 sec. rest; n=30). DC-MEG and tr-NIRS were recorded over the left motor cortex. In extension to recent modulation-based MEG recordings, unmodulated DC-MEG allows to characterise neurovascular physiology not only in the low frequency range but also simultaneously up to the millisecond range, which is important in particular at the beginning and end of activation. The present study demonstrated the feasibility of combined recordings in both age cohorts. Ongoing data analysis already demonstrated a rapid MEG onset and a much slower decay at the end of the movement period which can now be described in the relation to the NIRS signal on a scale of tenth of ms. Further group data analysis will show if there are significant age flow change leading to widespread cortical infarcts. It represents an inverse hemodynamic response to

related neurovascular coupling differences between both groups. This dual measuring technique provides a new non-invasive recording tool to prove also pathophysiological cerebral coupling concepts, e.g., in stroke, hypertension and Alzheimer's disease.

54 MOLECULAR MECHANISMS UNDERLYING AMYLOID BETA MODULATING EFFECTS OF FENOFIBRATE AND CELEBREX

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Amyloid ß (Aß) protein is produced by cleavage of the amyloid precursor protein (APP) by the beta-site amyloid precursor protein cleaving enzyme (BACE) and Presenilin (PS) 1 as the catalytic site of the gamma-secretase. Production of Aß as species of different length, mainly Aß40 and the highly fibrillogenic Aß42, depends on the precision of the PS1 cleavage site. ur previous data suggest that familial Alzheimer's disease (FAD) PS1 mutations increasing the Aß42/40 ratio cause a consistent alteration in PS1 conformation and that Aß42-lowering NSAIDs lead to inverse conformational changes. Several other compounds, e.g. fenofibrate and celebrex, have recently been reported to increase Aß42/40 ratio, the exact mechanism remains however unclear. The aim of this study is to determine if the increase in Aß42/40 ratio due to fenofibrate and celebrex treatment correlates with change in PS1 conformation, PS1/APP alignment, and/or subcellular distribution of the APP-PS1 complex. We used an established Fluorescent Lifetime Imaging Microscopy (FLIM) assay to monitor PS1 conformation and alignment of APP with PS1 in intact cells. Furthermore, we applied a novel FRET probe GFP-PS1-RFP fusion protein to monitor PS1 conformation in live cells. Biochemical approaches were used to investigate APP trafficking and processing. We found that fenofibrate and celebrex treatment significantly change PS1 conformation similarly to FAD PS1 mutations, and alter the alignment of APP with PS1. Using the GFP-PS1-RFP fusion protein we show that fenofibrate treatment significantly change PS1 conformation in live cells. Furthermore, fenofibrate treatment caused profound redistribution of APP within the cell. APP maturation was inhibited resulting in a decreased amount of APP on the cell surface, and full-length (FL) APP was targeted to the lysosomes. We conclude that a) the Aß42-raising effect of fenofibrate and celebrex correlates with the change in PS1 conformation and altered alignment of APP with PS1 similar to that of FAD PS1 mutations, and b) fenofibrate affects APP maturation and trafficking.

55 OLIGODENDROCYTIC COUPLING IN THE CNS WHITE MATTER RELATED TO CX47 EXPRESSION

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Connexins, the molecular components of gap-junctions, form connections between cells for cellular communication and thereby determine cellular properties. In the brain, Cx47 as well as Cx32 and Cx29 are expressed only in oligodendrocytes, the myelinating cells of the CNS. Several genetic diseases demonstrate that Cx32 and Cx47 are fundamental for the normal functionality of CNS and PNS myelin. Based on immunocytochemistry and recombinant studies, oligodendrocytes are not coupled among each other, but to astrocytes (Orthmann-Murphy et al., 2008, J Mol Neurosci.). To test for functional gap-junction coupling, we used the patch-clamp technique to inject gap-junction permeable dye. Oligodendrocytes were identified by their characteristic membrane current pattern and by their distinct morphology after dye injection. Injection of biocytin into a single oligodendrocyte in acute murine slices of corpus callosum (P10-15) via dialysis with the patch-pipette led to dye transfer to neighbouring cells in 94% of experiments (N=17). The dye spread in average to 43 cells. In Cx47 knock-out mice, biocytin spread to an average of four other cells in 73% of experiments (N=15). These data suggest that Cx47-deficiency did significantly affect the size of the network of coupled cells, but coupling is still present. To identify the cells coupled in the network we developed a method to combine biocytin labeling with CNPase and GFAP staining, markers for oligodendrocytes and astrocytes, respectively. In the corpus callosum of wildtype mice (P10-15), most biocytin labeled cells were CNPase positive (N=7). The CNPase-negative cells were not astrocytes since none of the biocytin-labelled cells were GFAP positive. These results indicate that oligodendrocytes in the corpus callosum are coupled among each other, but not to astrocytes.

56 DURATION OF CORTICAL SPREADING ISCHEMIA DEPENDS ON INTRACELLULAR CA^{2+}-STORES.

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Delayed ischemic neurological deficit (DIND) is one of the major complications after subarachnoid hemorrhage (SAH). It occurs in up to 40% of patients who survive the initial bleeding. About 13% develop delayed cerebral infarcts on CT. Based on experiments in rats, cortical spreading ischemia (CSI) has been proposed as a mechanism of DIND. CSI is a long-lasting, spreading wave of an ischemic blood

cortical spreading depolarization (CSD). In SAH patients CSD occur frequently and correlate positively with development of new infarcts if significantly prolonged (Dreier et al., Brain (2006), 129, 3224–3237). In rats CSI occurs when the Na^+ K^+ ATPase (NaK) activity and the NO concentration (e.g. due to nitric oxide synthase inhibition by L-NNA respectively) are simultaneously reduced in the subarachnoid space. Isolated inhibition of Alpha2 and Alpha3 isoforms of NaK is sufficient to induce CSI. It leads indirectly to increase of the cytoplasmic Ca^{2+} concentration and subsequently to filling of the Ca^{2+}-stores in the sarco/endoplasmic reticulum via the appropriate Ca^{2+}-ATPase (SERCA). Thus we tested, if depletion of these internal stores has an influence on the CSI. A closed cranial window was implanted in rats. Cerebral cortex was superfused with artificial cerebrospinal fluid (ACSF) containing L-NNA (1 mM). Subsequently, thapsigargin (TG), an inhibitor of the SERCA was added to the ACSF at concentration of 100 μM. Finally ouabain at 50 μM was applied. The CBF changes were monitored by Laser-Doppler-Flowmetry. During CSI CBF fell to about 50% of baseline value. TG did not prohibit hypoperfusion, but shortened it significantly to 1:16 (0:58 – 3:18) min (vehicle control 4:31(2:07 – 8:47)).

57 CHARACTERIZATION OF THE PERIPHERAL OSMORECEPTOR

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Peripheral osmosensitive-fibers are believed to be located in the liver and/or the hepatic branch of the portal vein and project to the CNS via hepatic nerves. They have not yet been visualized or functionally characterized, indeed the location and sensory origin of such fibers is not known. We show that in rats and mice drinking water leads to a decrease of blood osmolality in the portal vein by 25mOsm. We visualized activation of hepatic sensory fibers by immunostaining for phosphorylated ERK (extracellular-signal-related-kinase). The osmotic stimulus led to a robust induction of pERK in a sub-population of Isolectin B4-negative sensory nerve fibers. We made acute cultures of dorsal root ganglion neurons from the thoracic ganglia (T7-T13) a proportion of which innervate visceral tissues including the liver. Of these cells 31% show a robust increase in intracellular calcium following stimulation with hypotonic solutions (Fura-2 based calcium imaging). Sensory neurons taken from ganglia that do not innervate viscera had a significantly smaller number of osmosensitive cells. The Transient Receptor Potential Vanniloid 4 (Trpv4) is believed to play a role in osmosensation. Here we show using Ca-Imaging and patch clamp techniques a significant decrease in osmosensitive cells of Trpv4 -/- animals compared to WT only in the thoracic, but not in the cervical and lumbar region. We also examined a transgenic mouse in which the alpha-3 subunit of the nicotinic acetylcholinreceptor is fused to GFP (green fluorescent protein). We show, that ERK becomes activated in this subpopulation of GFP+ fibers in the liver after water intake. The percentage of GFP+ cells showing osmosensitivity in ca-imaging experiments was much higher than GFP- cells in thoracic ganglia. This animal model to study the activation of peripheral osmoreceptors may prove a valuable tool to dissect the physiological relevance of this sensory pathway.

58 THE POTASSIUM THRESHOLD FOR CORTICAL SPREADING DEPRESSION IS INFLUENCED BY AGE AND EPILEPTIC CHANGES IN RAT AND HUMAN NEOCORTEX

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Cortical spreading depolarization (CSD) is a wave of depolarization of neurons and glial cells, which is characterized by massive ion changes of the intra- and extracellular space and leads to suppression of neuronal activity. CSD is assumed to be the neurophysiological correlate of the migraine aura and occurs in ischemic stroke, subarachnoid hemorrhage and traumatic brain injury in all investigated vertebrates including humans. There is evidence that CSD contributes to neurodegeneration in tissue at risk and, thereby, to poor clinical outcome. CSD can be elicited by electric stimulation, chemical poisons or Na,K-ATP-ase blockade. Elevated extracellular potassium level such as in cerebral focal ischemia or after brain hemorrhage is another potent inducer of CSD. It was demonstrated before that chronically epileptic rats are more resistant to CSD induction than non-epileptic rats. Furthermore, it has been speculated that the human brain shows a higher resistance to CSD compared to rodents. We compared the K+ threshold for CSD in human and rat temporal neocortex. Human neocortical slices were obtained from surgery on chronically epileptic patients and compared to chronically epileptic aged rats as well as both young and aged control rats in order to estimate the impact of age and epilepsy on the lower susceptibility to CSD. The young control rats had the lowest threshold, followed by the aged control rats. The highest threshold was observed in epileptic rats and human tissue that did not differ from each other. Our results imply that both age and chronic epileptic changes in the neocortex decrease

the susceptibility to CSD under elevated potassium levels whereas no significant difference between the species was detected.

59 GABAB RECEPTOR MEDIATED INHIBITION IN MESIAL TEMPORAL LOBE EPILEPSY

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Mesial temporal lobe epilepsy (mTLE) is associated with an alteration in the balance of inhibition and excitation in the hippocampal network. GABA is the major inhibitory neurotransmitter in the brain, where it activates both ionotropic $GABA_A$ and matabotropic $GABA_B$ receptors ($GABA_BR$). The alterations in the expression or function of $GABA_BR$ have been reported in human epileptic patients. To identify changes in $GABA_BR$ mediated transmission in mTLE we performed experiments on chronic epileptic mice following a unilateral injection of kainic acid (KA) into the dorsal hippocampus. Transverse slices were obtained from ventral hippocampus of control and KA-injected mice. Extracellular and intracellular recordings were obtained from area CA3 of the hippocampus. Inactivation of hippocampal $GABA_BR$ with CGP55845A (1 μM) in chronic epileptic mice decreased the power of gamma frequency oscillation whereas it was unchanged in control mice. $GABA_BR$ agonist baclofen (5-10 μM) completely blocked KA-induced oscillations in control slices and caused transition from enhanced gamma frequency oscillations into the pathological activity in slices from epileptic animals. Intracellular recordings revealed opposite effects of baclofen on the firing properties of pyramidal cells: decreases in control and increases in epileptic mice. These effects were coinciding with the corresponding changes in the power of the gamma activity. Our results suggest that $GABA_BR$ mediated inhibition contributes to altered network oscillatory activity in a mice model of mTLE.

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Poster Presentations - Session II

Friday, June 6, 16.00 - 17.30
Saturday, June 7, 10.00 - 11.00

60 HEXOKINASE II - A GLUCOSE DEPENDENT MEDIATOR OF SURVIVAL

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Hexokinase II is one of the hexokinase isoenzymes facilitating the first step of glucose metabolism by phosphorylating glucose. Hexokinases have also been implicated in regulation of apoptosis. In particular, mitochondrial binding of hexokinases has been found to show apoptosis modifying features. This association is stabilized by Akt-kinase. Hexokinase II is located in the outer mitochondrial membrane. This localization may function as a link of metabolism and apoptosis. We found upregulation of Hexokinase II mRNA as a response to ischemic preconditioning in cultured rat cortical neurons. To investigate whether this response promotes survival, we studied protective features of hexokinase II in an in vitro model of cerebral ischemia. Employing a novel electroporation approach, hexokinase II was transfected in embryonic rat cortical neurons. Cultures were submitted to oxygen-glucose-deprivation (OGD), oxygen deprivation (OD) and glucose deprivation (GD), respectively. Compared to controls, Hexokinase II protected transfected neurons from damage in OGD and OD experiments but showed detrimental effects on neurons in GD experiments. We present clear evidence for glucose-dependent survival mediated by hexokinase II.

61 ROLE OF DIFFERENT CTL-EFFECTOR MOLECULES IN DAMAGING THE NEURO-AXONAL UNIT IN VIVO

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The importance of cytotoxic T cells (CTLs) in virus-induced immunopathology is widely acknowledged

and also their role as effectors in autoimmune diseases of the CNS has become increasingly recognized. With regard to neurons as a target for CTLs, evidence was provided for antigen-specific interaction by MHC class I restricted $CD8^+$ T cells with neurons *in vitro*. However, the case for epitope-specific interaction of CTL with neurons *in vivo* is less well established and remains controversial. We recently established and characterized a new animal model that allows the analysis of molecular requirements of CTL neuroaxonal interaction *in vivo* (Merkler et al., J. Clin. Invest., 2006): Neonatal infection (first hit) with a genetically engineered and attenuated lymphocytic choriomeningitis virus (rLCMV/INDG) resulted in viral persistence exclusively in CNS neurons. Second infection in adulthood (second hit) with a LCMV Cl13 strain (LCMV Cl13) triggered a vigorous $CD8^+$ T cell response of antiviral specificity that resulted in severe CNS inflammation in rLCMV/INDG-carrier mice. In the present work, we dissected the contribution of different CTL effector molecules Perforin, FAS-Ligand, Interferon-γ (IFN-γ) and TNF-α in mediating acute neuronal damage in vivo. Histopathological analysis indicated that CTL-derived IFN-γ but not FAS or Perforin are essential for the development of dendritic and synaptic alterations and consequently disease precipitation during CTL-neuron engagement in vivo.

62 MODULATION OF THERMAL NOCICEPTION BY NGF AND SCF/C-KIT SIGNALING

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Sensory neurons in the DRG transduce diverse sensory sensations like touch, heat and pain. Unmyelinated C-fiber axons represent about 60% of DRG population and most are polymodal responding both to noxious thermal and mechanical stimuli. Neurotrophins are known to be involved in determing the final phenotype of sensory neurons. To target the nociceptors the effect of NGF was suppressed in the early postnatal period by injecting blocking antibodies to NGF. This treatment led to a permanent change in the phenotype of cutaneous sensory neurons by changing the relative proportion of Aδ-delta-fibers and polymodal C-fibers. In addition CMH fibers had elevated thermal thresholds (5°C higher than controls). Treated mice also displayed behavioral thermal hypoalgesia. DRGs were used for gene chip expression analysis, and revealed 260 regulated genes in anti-NGF treated DRGs compared to controls. Large-scale in-situ analysis showed that some of these transcripts were expressed in sub-populations of DRG neurons. One of these genes - the receptor tyrosine kinase c-Kit - was functionally characterized. In DRG c-Kit is predominately expressed in small diameter cells expressing TrkA and CGRP. Mice lacking a functional c-Kit receptor displayed profound thermal hypoalgesia attributable to a marked elevation in the thermal threshold and reduction in spiking rate of CMH nociceptors. Activation of c-Kit by SCF induced a profound potentiation of heat-activated currents in 50% of isolated heat sensitive small diameter neurons. Acute application of SCF induced thermal hyperalgesia in mice and this action required TRPV1. SCF could potentiate capsaicin induced Ca^{2+} signal in a subpopulation of capsaicin sensitive cells. Thus, SCF/c-Kit signaling system has a key role in setting the thermal threshold for activation of heat sensing nociceptive neurons.

63 ANALYSIS OF OPIOID RECEPTOR/ K^+ CHANNEL COUPLING IN SENSORY NEURONS

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Opioids are the most effective and widely used drugs in the treatment of severe pain. They act through G-protein-coupled receptors located on central and peripheral sensory neurons. Three classes of opioid receptors (mu, delta, kappa) have been identified. Several mechanisms are involved in opioid analgesia including G-protein-gated inwardly rectifying K^+ (GIRK) channel activation and inhibition of 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. The GIRK channels form homo- or heterotetrameric complexes, and are known to support the inhibitory effects of opioids in the central nervous system. The subunits GIRK1 and 2 have been found to be expressed within the spinal cord dorsal horn, the cerebellum, the hippocampus and the cortex. We are interested in whether GIRK channels are present and whether opioids are coupled to GIRKs on peripheral sensory fibers. Furthermore, we will investigate the role of GIRK/opioid receptor coupling in a mouse model of inflammatory and neuropathic pain. To approach these questions, we are currently performing quantitative RT-PCR, western blot and patch clamping experiments. We found no significant expression of all 4 GIRK subunits in sensory neurons using RT-PCR and western blot. No change in the expression level could be observed after inflammation of the mouse hindpaw. We also investigate functional coupling of GIRK channels and opioid receptors in peripheral sensory neurons using Patch clamping. We found no evidence for inward rectifying currents in mouse DRG neurons, either before or after treatment with GIRK agonist DAMGO. Our data indicate that GIRK channels are not present in sensory neurons and do not contribute to peripheral analgesia under normal and inflamed conditions.

64 DOES ENDOTHELIN-1 INDUCE CORTICAL SPREADING DEPOLARIZATION (CSD) VIA A DIRECT EFFECT ON THE VASCULATURE?

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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 one of the most potent vasoconstrictors. Moreover, it potently induces CSD in vivo. ET-1 has been related to several pathophysiogical states in animals and humans associated with the occurrence of CSD including subarachnoid hemorrhage, ischemic stroke and traumatic brain injury. The mechanism by which ET-1 induces CSD is scarcely understood. In order to analyze whether induction of CSD by ET-1 is mediated by its vasoconstrictive effect, we used a two cranial window model in rats (n=11). ET-1 was brain topically applied in one window while the second one served as control. DC/AC-electrocorticography (ECoG) and laser-Doppler flowmetry were used to detect CSD. We observed a cluster of CSD 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±2.2mV on which transient negative DC shifts of CSDs were riding. This was accompanied by a positive DC shift of 0.9±0.9mV in the control window superimposed with transient negative DC shifts. In another six experiments we recorded the pH changes associated with ET-1-induced CSD using pH-sensitive microelectrodes exhibiting initial acidification followed by a sharp alkaline shift typical of ischaemic CSD. The pial arteries were imaged onto a camera to assess whether significant vasoconstriction precedes ET-1-induced CSD. This was typically observed in some arteriolar segments. A detailed analysis is currently performed off-line using Image-J software. In conclusion, our preliminary data support the notion that ET-1 induces ischaemic CSDs due to its vasoconstrictive action.

65 RHOG IS A TARGET FOR MI-RNA DEPENDENT REGULATION OF EXPRESSION AND HAS AN IMPACT ON AXONAL BRANCHING

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RhoG is a member of the Rho family of small GTPases. It was shown to be involved in the regulation of immune function, in processes of cell migration, phagocytosis, and neurite outgrowth induced by nerve growth factor. RhoG activates Rac1 via a ternary complex containing ELMO and Dock180. The expression of RhoG in the brain is developmentally regulated. One peak of expression in the rat cerebral cortex is around embryonic day 16. After declining, RhoG message is then upregulated again around postnatal day 20. Although functional studies in neuronal cell lines suggested RhoG to be important for neurite outgrowth, its functional role in primary neurons is not clear. Here we show that, in contrast to neuronal cell lines, RhoG does not seem to be involved in axonal outgrowth of primary hippocampal neurons. However, RhoG negatively regulates axonal branching. Further, we bring evidence that RhoG expression is regulated by the neuronal microRNA miR-124, and that this regulation has functional consequences for axonal branching.

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66 THE FUNCTION OF THE COXSACKIEVIRUS-ADENOVIRUS RECEPTOR (CAR) IN THE DEVELOPING NERVOUS SYSTEM – ITS SELF-ASSOCIATION AND INTERACTION WITH ECM GLYCOPROTEINS

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The coxsackievirus-adenovirus receptor (CAR), a transmembrane protein and member of the immunoglobulin superfamily, is strongly expressed in the developing central nervous system and is possibly involved in the formation of synapses or axonal outgrowth. Antibodies to CAR block attachment of neurons on glycoproteins of the extracellular matrix (ECM) or disturb neurite extension on basal laminae preparations and in eye organ cultures. Binding studies and affinity isolation of native CAR showed that fibronectin, laminin, fibulin-1, tenascin-R are extracellular interaction partners of CAR. Interestingly the affinity of recombinant CAR to fibronectin is even higher (K_d: 100nM) than the affinity to the fiber knob protein of the adenovirus (K_d: 140nM). We mapped the interaction to the heparin2/fibulin-1 binding-domain of fibronectin (283aa), which is different from the main integrin binding-segment, and to the second immunoglobulin-domain (D2) of CAR. Surprisingly, we observe homophilic binding of CAR only when it is glycosylated, whereas heterophilic binding is also detected when recombinant CAR is expressed in bacteria. Beside the CNS, CAR is also expressed on myotubes and through its interaction with agrin it might be crucial for the generation of the neuromuscular junction. We assume that CAR acts, like integrins, as a linker

between the ECM and the actin-cytoskeleton. We found that alpha-actinin is an intracellular binding partner of CAR. In mice deficient for CAR, the formation of the actin cytoskeleton is impaired.

67 CORTICAL GLUTAMATE IS LINKED TO REWARD RELATED VENTRAL STRIATE ACTIVITY – A COMBINED FMRI AND 1H-MRS STUDY

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Processing of rewarding stimuli is associated with increased firing rate of dopamine neurons in the ventral striatum, a core region of the brain reward system. A close interaction between dopamine and glutamate has been proposed to play an important role in reward processing and in the pathophysiology of schizophrenia. A correlation between the activity of the ventral striatum (BOLD contrast during reward processing) and glutamate concentration in the anterior cingulate cortex in healthy subjects is hypothesized. 22 healthy subjects (age 19 to 46 years) participated in a combined fMRI and MRS experiment. In healthy subjects positive anticipation led to robust bilateral activation in the ventral striatum. Within the region of interest, multiple regression analysis shows activation in a cluster of 73 voxels on the left side and 23 voxels on the right side to be negatively correlated with the concentration of glutamate in the ACC. No significant positive correlations were observed and no significant correlations (positive or negative) were observed for the hippocampal glutamate concentration. Our results may indirectly visualize an interaction of dopaminergic and glutamatergic neurotransmission which would be highly relevant for schizophrenia research.

68 COMBINED ANTIDEMENTIVE TREATMENT IMPROVES COGNITIVE ABILITIES ONLY IN MCI-AD

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Mild cognitive impairment (MCI) may represent early stages of different neurodegenerative diseases. The majority of the amnestic subtype (aMCI) is thought to represent a prodromal stage of Alzheimers disease (AD). In a double-blinded placebo-controlled study 237 aMCI were randomized to receive a combination therapy of Galantamin plus Memantine (Gal/Mem), Galantamine alone (Gal) or placebo (Plc). The study was prematurely stopped during recruitment for safety reasons, at that time aMCI were treated between 56-346 days. ADAS-cog was repetitively administered while patients received study medication and after discontinuation of treatment. 83 patients were reexamined two years after study entry. Analyzes of the etiologies underlying the aMCI syndrome revealed that only patients with probable AD (MCI-AD) showed a significant cognitive benefit, while other etiologies improved only moderately. Improvement in the Gal/Mem group measured by ADAS-cog exceeded the effect of treatment with Gal alone, while patients receiving Plc worsened (Gal/Mem: 1,08±5,38, Gal: 0,29±2,67, Plc: -2±3,27; ▲ from baseline; six months of treatment). After discontinuation of treatment with Gal MCI-AD showed a significant cognitive decline (MCI-all: -1,82±4,85, MCI-AD: -2,67±3,5, ▲from discontinuation baseline). Discontinuation of Mem showed no immediate worsening in ADAS-cog within one week. Two years after the study had started 15% of aMCI had converted to dementia, all of them belonged to the MCI-AD subgroup and the majority of converters was positive for APOE ε4. We conclude that only MCI-AD show a significant cognitive improvement and the combination therapy (Gal/Mem) exceeded the monotherapy (Gal

69 NKCC1-DEPENDENT GABAERGIC EXCITATION DRIVES SYNAPTIC NETWORK MATURATION DURING EARLY HIPPOCAMPAL DEVELOPMENT

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Due to a high intraneuronal chloride concentration GABA acts depolarizing in the immature brain and is thereby thought to sculpture the developing neuronal network. We show that GABA-triggered depolarization and Ca^{2+}-transients were attenuated in mice deficient for the Na-K-2Cl co-transporter NKCC1. Correlated Ca^{2+}-transients and giant depolarizing potentials (GDPs) were drastically reduced and the maturation of the glutamatergic transmission in CA1 delayed. Brain morphology, synaptic density, and expression levels of selected developmental marker genes were unchanged. These data show that NKCC1-mediated Cl^- accumulation contributes to GABAergic excitation and network activity during early postnatal development and thus accelerates the maturation of excitatory synapses.

70 FUNCTIONAL EFFECT OF A MUTANT OF THE SECOND EXTRACELLULAR LOOP OF CLAUDIN-5 IN THE BLOOD-BRAIN BARRIER

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Tight junctions (TJs) of endothelial and epithelial cells are the most apical component of the junctional complex. They seal the paracellular space thus separating different compartments for solutes. TJ are organized as a network of intramembranous strands, which are mostly comprised of claudins, occludin and junctional adhesion proteins. Studies on knock-out mice have demonstrated that Claudin-5 (Cld5) tightens the blood-brain barrier (BBB). To investigate the role of selected amino acids of the second extracellular loop (ECL2) of Cld5 in tightening the paracellular space, we stably transfected Cld5-free MDCKII cells with $Cld5_{wt}$ or $Cld5_{Y148A}$. The mutant owed a loss of trans-interaction between Cld5 oteins in the plasma membrane of opposing cells. functionally characterize the impact of the itation, we measured the transepithelial electrical istance (TER) of the transfected cells using two ferent techniques. First, cells were seeded directly to gold electrodes of the ECIS system. We did not tect a significant difference between the tightness $Cld5_{wt}$-and $Cld5_{Y148A}$-expressing cells. Second, cells were seeded on filters allowing TER asurements with a conventional voltohmmeter. In ntrast to the ECIS system, a significantly higher R was measured for $Cld5_{wt}$ than for $Cld5_{Y148A}$. rthermore, when compared to mock controls, flux of fluorescein and 10°kDa FITC-dextran asured for $Cld5_{wt}$ and $Cld5_{Y148A}$ transfected cells was decreased and increased, respectively. These results indicate that (i) for our investigations the ECIS system is less sensitive than conventional techniques. (ii) As Y148 is a key amino acid in the aromatic binding core of Cld5-ECL2 causing the trans-interaction, this interaction is involved in the tightening mechanism of the paracellular space of the BBB.

71 TOOLS FOR THE GENERATION OF SPECIFIC DRG CELL STRUCTURES IN VITRO.

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The cells of the dorsal root ganglion (DRG) exhibit a distinct morphology in vivo, with a single axon that bifurcates at the dorsal root entry zone into two arms. However, acutely cultured DRG cells do not spontaneously form similar structures in vitro. We are using microcontact printing to pattern laminin on glass surfaces to culture cells in vitro with a structure similar to that observed in vivo. Microcontact printing of proteins can be used to print proteins in specific patterns at the micrometer scale. Printing of laminin on glass coverslips generates precise laminin structures that are 10 nm in height. DRG cells can be successfully cultured on printed laminin, with the cells avoiding the non-printed areas and the resulting cell shapes determined by the underlying pattern, including branching of neurites that are grown on laminin printed in a T-junction structure. As well as 2D patterns, the technology used to create the masters used for microcontact printing can also be used to generate masters for the formation of substrates for cell culture that include 3D topographical features. Such tools allow questions about the influence of cell structure on function to be addressed.

72 SIRT1 CRITICALLY CONTRIBUTES TO THE REDOX-DEPENDENT FATE OF NEURAL PROGENITORS

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In the adult mammalian brain, multipotent and self-renewing neural progenitor cells (NPCs) have the capacity to generate new neurons, astrocytes and oligodendrocytes. NPCs may thus serve as a regenerative tool with which brain damage can be compensated. However, repair processes in response to many forms of neuronal injury, be theyinflammatory, ischemic, metabolic, traumatic or other, are characterized by a failure to replenish neurons and by a predominant occurrence of astrocytes (known as astrogliosis). The possible molecular pathways underlying this phenomenon are only poorly understood. Here, we show that subtle alterations of the redox state, found in different brain pathologies, substantially regulate the fate of murine NPCs via the histone deacetylase *silent mating type information regulation 2 homolog 1* (Sirt1). Mild oxidative conditions or direct activation of Sirt1 suppressed proliferation of NPCs and directed their differentiation towards the astroglial lineage at the expense of the neuronal (and *vice versa*). Under oxidative conditions *in vivo* and *in vitro*, NPCs upregulated Sirt1, which then bound to the basic helix-loop-helix (bHLH) transcription factor *Hairy/enhancer of split 1* (Hes1) and subsequently inhibited the proneuronal bHLH transcription factor *mammalian achaete scute homologue 1* (Mash1). Knock-down of Sirt1 by in utero electroporation of NPCs prevented oxidation-mediated suppression of neurogenesis, and upregulated Mash1 *in vivo*. Our results provide evidence for an as yet unknown metabolic master switch which determines the fate of neural progenitors.

73 CIRCADIAN RHYTHM IN PHONETIC SPEECH PERCEPTION

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Some studies found time-dependent variation of cognitive performance which was separate from lapses in attention and psychomotor slowing (see Schmidt et al. 2007). This could suggest circadian rhythm in cognitive functions. Our study investigated differences in speech processing, in particular speech perception, during the circadian cycle. Based on the theory of Borbély (1982, see Schmidt et. al 2007) we predicted an increase of performance after a circadian nadir independent of vigilance and sleepiness. Twelve subjects performed a behavioural discrimination task in a forced choice paradigm every 3h during 40h of sustained wakefulness (Constant Routine protocol). Acoustic and phonetic stimuli were presented binaural via headphones. Subjective sleepiness was determined hourly, psychomotor vigilance every three hours. Salivary melatonin and body temperature were used as circadian phase marker. Best speech performance was found in the evening which was positive correlated with body temperature. After the circadian nadir associated with a central slowing without correlation of vigilance or sleepiness in the early morning performance increased again with a positive peak in the evening. We interpret this fact as a circadian drive. Longer reaction times and more lapses in phonetic perception indicate a higher task difficulty and a higher cognitive level compared to acoustic performance. In conclusion, these results confirmed our hypothesis of circadian oscillation in speech processing, in particular in speech perception, which could open a new direction for research of causes of language disorders.

Schmidt C et. al (2007). A time to think: Circadian rhythms in human cognition. In: Cognitive Neuropsychology 24 (7): 755-78

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74 DIFFERENCES IN REWARD PROCESSING ACROSS THE LIFESPAN

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Individuals use the outcomes of their actions to adjust future behavior, and differential responses to both gains and losses have been proposed across the lifespan. On a neurophysiological level, differential activation patterns in the striatum during reward processing have been shown in older adults. At the same time, conceptual frameworks from developmental psychology suggest that fundamental changes in motivational structure and reward processing may occur as early as midlife. We used event-related functional magnetic resonance imaging to determine whether young and middle-aged adults differed in both self-reported and neural responsiveness to anticipated gains and losses. The present study provides evidence for intact striatal activation during gain anticipation in both groups, but shows a relative reduction in activation during gain anticipation in middle-aged adults. Furthermore, striatal activation during gain anticipation was related to measures of fluid intelligence. These findings suggest that changes in the processing of gains and losses across the lifespan are reflected by functional changes as early as midlife, and may be related to general losses in fluid intelligence. Implications for decision-making are being discussed.

75 ASTROCYTES RESPOND TO THE CALYX OF HELD ACTIVITY

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The medial nucleus of the trapezoid body located in the brainstem is involved in sound localization and contains the calyx of Held synapse (CoH), an axo-somatic giant synapse. Here we study the physiological properties of astrocytes and their interaction with CoH. Astrocytes were easily identified in GFAP/eGFP transgenic mice. Whole-cell recordings showed a linear current-voltage relationship (I-V) when repetitive de- and hyerpolarising 50 ms voltage pulses where applied. When biocytin was included in the pipette, the dye spread to a network of cells indicating that astrocytes are coupled. D-Asp (0.5 mM) triggered an inward current in astrocytes and this response was partially blocked by TBOA (100 μM) suggesting the expression of glutamate transporters. Kainate (0.5 mM) mediated responses were blocked by CNQX (25 μM) indicating the expression of AMPA/kainate receptors. Stimulation of the afferent fibers to the MNTB also triggered a response in astrocytes, namely a slow inward current and an intracellular calcium increase. When astrocytes were depolarised by voltage steps (from -70 to +50, the amplitude of the spontaneous postsynaptic currents recorded in neurons was increased, suggesting a modulation of the CoH by astrocytes. To identify astrocytic compartments at the electron microscopic level, the eGFP/GFAP transgenic mice were labelled using antibodies against

eGFP. Fine processes of astrocytes contact both, the pre- and postsynaptic membrane, but synaptic-like structures were never observed. These results show that astrocytes sense CoH activity and modulate the response in the postsynaptic cell.

76 K_v7 (KCNQ) POTASSIUM CHANNEL OPENERS ATTENUATE LEVODOPA-INDUCED DYSKINESIAS IN 6-OHDA-LESIONED RATS

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Levodopa-induced dyskinesias (LID) represent a severe complication of long-time pharmacotherapy in Parkinson's disease that deserves novel therapeutics. In the present study, the effects of the $K_v7.2$-7.5 channel openers retigabine and flupirtine were examined in comparison to amantadine (positive control) in a rat model of LID. Compared with vehicle controls, retigabine (2.5, 5 mg/kg i.p.) and flupirtine (10 mg/kg i.p.) administered prior to levodopa significantly reduced the severity of levodopa-induced abnormal involuntary movements (AIM). The antidyskinetic effect of retigabine (5 mg/kg) was comparable to this of amantadine and was not accompanied by severe adverse effects. The $K_v7.2$-7.5 channel blocker XE-991 did not exert any effects on AIM at a dose of 1.5 mg/kg i.p., but antagonised the antidyskinetic effects of retigabine. At a higher dose of 3 mg/kg, XE-991 increased the dystonic component of AIM. The results suggest that K_v7 channel openers, which have been reported to exert antiparkinsonian and analgetic effects, could represent interesting candidates for the treatment of LID. The antidyskinetic efficacy of the activators of $K_v7.2$-7.5 channels might be related to a suppression of neuronal activity in the striatum. Further studies are under the way to clarify whether retigabine and flupirtine delay or prevent the development of LID.

77 INTERLEUKIN—1BETA AND NEUROTROPHIN-3 APPLICATION FOR THE TREATMENT OF SPINAL CORD INJURY

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Traumatic injury of the spinal cord is followed by a neuroinflammatory wound healing response. Previously, we demonstrated that pro-inflammatory cytokines influence neurotrophin-induced axonal outgrowth of dorsal root ganglia in a dose-dependent manner. In the present study, we address the question of whether cytokines modulate neurotrophin-induced axonal regeneration after CNS injury in vitro and in vivo. Using an organotypic cortex outgrowth assay, we demonstrated that neurotrophin-3 (NT-3) and the pro-inflammatory cytokines IL-1beta (IL-1b), IL-6 and TNF-alpha significantly promote axon elongation and density. The combination of recombinant IL-1b and NT-3 significantly stimulate axon outgrowth compared to NT-3 alone. Interestingly, IL-1b deficiency had no influence on axon growth suggesting that endogenous IL-1b is not necessary for spontaneous neurite elongation. Recombinant IL-1b significantly increased the axonal length of primary neurons, indicating a direct effect on neuronal cells. In a similar outgrowth assay using organotypic transverse slices of mouse E13 spinal cords IL-1b and NT-3 could not increase axonal outgrowth. However a significant inhibition of axon growth by the pan-neurotrophin receptor blocker K252a suggests that maximal outgrowth is already induced by endogenous neurotrophins. Furthermore, we investigated the impact of IL-1b on NT-3 therapy after spinal cord injury (SCI) in vivo. NT-3 has already been successfully applied in several in vivo models of SCI, leading to axonal sprouting und functional recovery in rats. Thus, we established a mouse model of NT-3 therapy after contusion SCI. The local application of IL-1b was lethal, however, IL-1b deficient mice with and without NT-3 administration showed significantly better clinical outcome after SCI compared to wildtype control mice.

78 A SELF-MADE MEDIUM SUPPLEMENT FOR PRIMARY NEURONAL CULTURE REVEALS THE ROLE OF SELENIUM FOR NEURONAL SURVIVAL

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Mice with compromised selenoprotein expression in neurons suffer neurodegeneration. Selenoproteins are proteins containing the rare amino acid selenocysteine. There are 24 genes encoding selenoproteins in the mouse, most of which are neuronal expressed. Selenoprotein expression is most prominent in hippocampal, cortical, and cerebellar neurons. The selenium transport protein, selenoprotein P has been purified as a neurotrophic factor from calf serum, but can be functionally replaced in culture by sodium selenite, a common, but non-physiological, supplement for neuronal cell culture. Investigating the roles of selenoproteins in neurons is hampered by the fact that commercial B27 supplement contains selenite and a cocktail of other antioxidants, including enzymes like catalase and superoxide dismutase. To establish a cell culture model suitable for the study of selenium effects in

neurons, we have re-investigated the constituents of B27 and show that our self-made supplement yields comparable survival rates as B27. We show that the EC50 value of H_2O_2 is only about 40μM in medium lacking catalase as compared to 300μM in medium containing catalase (as B27). Moreover the effect of gene inactivation of Gpx4, a selenium-dependent phospholipid hypdroperoxide peroxidase, is masked in neurons by excess vitamin E in the culture medium.Using several inductors of cell death in vitro, like H_2O_2, glutamate or SIN-1, we demonstrated the profound modulation of cell survival by selenium content of the culture medium. In summary, we have now established a unique cell culture model in which we can dissociate the effect of selenium and other antioxidants from each other. In contrast, such studies are not feasible using commercial media already containing a high-dose mix of antioxidants.

79 COMBINATION OF DC-MAGNETO-ENCEPHALOGRAPHY AND TIME-RESOLVED NEAR-INFRARED SPECTROSCOPY FOR THE STUDY OF NEURO-VASCULAR COUPLING

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The knowledge of the temporal relation between neuronal activity and the accompanying response in the vascular system of the brain may foster a better understanding of fMRI in basic research and clinical applications. To this end, we have combined DC-magnetoencephalography (DC-MEG) and time-resolved near-infrared spectroscopy (trNIRS) to measure simultaneously cortical neuronal and vascular activations during finger movements in 12 subjects. In contrast to earlier studies, the modulation DC-MEG has been replaced by a broadband unmodulated DC-MEG and the temporal resolution of the combined setup is refined up to tens of ms. The subjects were asked to repeat a sequence of 30 s of finger movements followed by 30s of rest for 30 times. Independent component analysis (ICA) was applied to extract the stimulus related signal components at 0.0166 Hz (1/ 60 s^{-1}) from the DC-MEG and trNIRS data. ICA extracted the stimulus related signal best if the bandwidth of the data was reduced to 8 Hz. This indicates that the ICA assumptions are violated by, e.g., noise contributions or a number of additional sources above 8 Hz such as alpha-oscillators. This bandwidth reduction still allows to study the relevant processes as the transition time for the neuronal DC-MEG signal between rest and movement period is around 0.5 s contrasting with a transition time of several seconds in the vascular signals recorded by trNIRS.

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80 DRUG RESISTANCE IN THE HUMAN EPILEPTIC HIPPOCAMPUS AND TEMPORAL CORTEX

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Epileptiform activity could be induced in the dentate gyrus (DG) of hippocampal slices from surgically removed tissue of patients suffering from drug resistant mesial temporal lobe epilepsy (MTLE) (Gabriel et al. 2004). Furthermore, we showed that the in vitro-epileptiform activity in the DG – like seizures of long-time drug resistant MTLE-patients - is resistant to the antiepileptic drug carbamazepine (Jandova et al. 2006). In the present study we investigated effects of valproate (VPA, 1mM) and carbamazepine (CBZ, 50μM) on epileptiform activities in two different hippocampal regions (DG, Subiculum: 10-12mM [K+]o) and in the temporal cortex (TCx) (8mM [K^+]o and 50uM Bicuculline). Data were obtained from 120 recordings (32 patients). After 30 minutes perfusion with CBZ or VPA, epileptiform activity was completely suppressed in 3.3% of recordings (6.3% of patients). Ictal-like activity was replaced by inter-ictal spiking in 6.7% of recordings (3.1% of patients) or remained unaltered in 90% of recordings (90.6% of patients). In the last sample, event-amplitudes were slightly but significantly reduced while drug effects on event-duration, intra-event discharge frequency, and event-rate could not be proven significant. There were no differences of effects between hippocampus and TCx and between CBZ and VPA, indicating that focal epileptic tissue with open blood brain barrier is drug resistant on behalf of mechanisms located in the parenchyma.

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81 TOLL-LIKE RECEPTOR 4/MYD88 PATHWAY MEDIATES THE MICRO-GLIAL PROINFLAMMATORY RESPONSE TO THROMBIN-ASSOCIATED PROTEIN COMPLEXES

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Thrombin, the central blood coagulation factor, exerts a multitude of cellular effects through limited proteolysis of protease-activated receptors (PAR). This mechanism is also considered for the induction of proinflammatory mediators in microglia. Challenging this notion, we identified a minor high molecular weight (HMW) protein fraction as the sole and extremely potent carrier of this activity in thrombin preparations. The HMW fraction contains mature ¾ yet enzymatically inactive ¾ thrombin presumably within a plasma/coagulation protein complex. We show now that microglial activation by thrombin^{HMW} critically depends on Toll-like receptor 4 (TLR4) and associated MyD88 signaling, with additional receptor/signaling pathways providing contributions. On the other hand, PARs, alternative thrombin receptors, proteolytic thrombin activity and functional domains are either not mandatory or even dispensable. Biochemical analyses, mass spectrometry and functional characterization revealed fibronectin as a microglia-stimulating thrombin^{HMW} constituent with TLR4-agonistic capacity. Importantly, bacterial lipopolysaccharide as a common microbial TLR4 agonist can be ruled out as a confounding contaminant. Our findings identify the essential ligand-receptor mechanism underlying the thrombin/PAR-assigned proinflammatory responses in microglia. They may request a careful revision of other cellular activities previously established for thrombin. Most importantly, they indicate a role for TLR4-centered signaling in the activation of microglia by plasma-derived protein complexes upon vascular impairment. This novel mechanism especially supports the emerging concept of coagulation cascade-driven CNS damage in diseases like multiple sclerosis.
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82 NONVIRAL TRANSFECTION ENABLES STABLE GENE TRANSFER INTO MURINE MESENCHYMAL STEM CELLS DERIVED FROM BONE MARROW

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Mesenchymal stem cells (MSCs) from bone marrow have been used for therapeutic purposes in a variety of mouse models for neurological disorders. Powerful technologies for genetic modification of these cells offer their potential use in regenerative medicine and cyto –and gene therapy. MSCs were isolated from bone marrow of adult C57BL/6 mice and were characterized by their differentiation potential into adipocytes, osteoblasts and chondrocytes and by FACS analysis for their surface marker expression. We aimed to determine whether mMSCs can be genetically modified by ex vivo gene delivery using the following transient transfection procedures: nucleofection, magnetofection and lipofection. mMSCs were transfected with the pEGFP-N2 plasmid vector and were analysed by FACS for EGFP signalling 48hr after transfection. Results indicate that nucleofection is the most efficient procedure for transient gene delivery into mMSCs, followed by magnetofection and lipofection. By selection with G418 disulfate and use of single cell – colony forming unit (sc-CFU) assay transiently transfected mMSCs became stably transfected for EGFP by all three transfection methods without loss of their stem cell plasticity. Moreover, murine erythropoietin (mEPO) was introduced into mMSCs. Cells stably integrated mEPO into their genome and secreted high amounts of mEPO for several weeks as detected by ELISA. Hematopoietic activity of mMSC derived mEPO was successfully assessed by CFU-E (colony forming unit – erythroid) assay. In summary, transient transfection methods are sufficient to generate stable transfected mMSCs that might be a source to develop treating strategies of a variety of disorders like stroke, parkinson´s disease or myocardial infarction.
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83 ASTROCYTES IN SITU RESPOND TO THE ANTI-DEPRESSANT CITALOPRAM INDEPENDENT FROM NEURONAL ACTIVITY

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An active role for astrocytes in memory processing is more and more recognized, but their role in mood disorders has yet to be elucidated. The pathophysiological basis of major depressive disorder (MDD) and the mode of action of anti-depressant drugs are not completely understood. One important target in the treatment of MDD is the serotonine (5-hydroxytryptamine, 5-HT) system and selective serotonine reuptake inhibitors (SSRIs) are widely used to treat the disease. Interestingly, for astrocytes, a dysfunction in glutamatergic pathways was found in MDD. We loaded astrocytes in acute slices of the mouse prefrontal cortex with the calcium-sensitive dye Fluo-4 and analyzed the astrocyte calcium responses to stimulation with the SSRI citalopram or 5-HT directly. We found that in acute slices of the mouse prefrontal cortex, citalopram, as well as 5-HT itself induce calcium signals in a subset of astrocytes also in the presence of tetrodotoxin (TTX). The calcium transients in individual astrocytes occur delayed and not all at once, in contrast to responses

to ATP or glutamate. These delayed calcium responses were also observed after the application of the 5HT1- and 5HT2-receptor agonists 5-Carboxyamidotryptamine and alpha-Methyl-5-hydroxytryptamine, respectively. Responses to 5-HT could mostly not be evoked twice. This effect was diminished in the presence of TTX, and we determined glutamate as a modulatory substance: 1) after a calcium response evoked by glutamate, astrocytes do not show a response to 5-HT and 2) application of CNQX restores the ability to exhibit a second response to 5-HT. Thus, responses to stimulation of glutamatergic and serotonergic receptors on astrocytes are functionally interfering and astrocytes might link serotonergic and glutamatergic functions in the pathophysiology of MDD.

84 EVALUATION OF THE RAT FREE EXPLORATORY BEHAVIOUR AS AN ANIMAL TEST FOR TRAIT ANXIETY IN RATS

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The free exploratory paradigm is regarded as a reliable test for trait anxiety in mice (Griebel et al., Behav Pharmacol 1993, 637-644) but it may be useful in the research for the neurobiological basis of anxiety in rats, too. Previously we could show that rat strains differ in their desire for non-forced exploration of novel areas, like the surroundings of their familiar cage when the grid-covers of the cage were removed (Rex et al., Pharmacol Biochem Behav 1996, 107-11). Now, we evaluated this test behaviourally using naïve Sprague Dawley and Wistar rats obtained from different sources. Sprague Dawley rats were tested at the age of 30, 55, 78 and 110 days. Evaluation also included assessment of seasonal variation, sex-specific impact and habituation to the test. Additionally, the test was evaluated pharmacologically using diazepam (1, 2 mg/kg IP) and caffeine (50 mg/kg IP). Parameters measured: The latency to the first escape within 10 min, the percentage of rats exploring the outside and the number of the escapes. Latency to the first escape was the most reliable and sensitive parameter. Seasonal variability of the latency to the first escape was low. Rat strains and sexes differ in the latency too, while age-related differences have less impact. Diazepam (2 mg/kg) decreased and caffeine (50mg/kg) increased the latency to explore the outside of the cage. We conclude that the free exploratory behaviour can be used to study anxiety-related behaviour in rats.

85 STIMULUS DEPENDING CHANGES OF EXTRACELLULAR GLUCOSE IN THE RAT HIPPOCAMPUS DETERMINED BY IN VIVO MICRODIALYSIS

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Neuronal activity is coupled to brain energy metabolism with glucose being an important substrate. We assessed extracellular glucose concentrations in the rat ventral hippocampus during anxiety-related behaviour. Determination of basal hippocampal glucose and lactate/pyruvate ratio in male Wistar rats was conducted in the home cage using *in vivo* microdialysis. Rats were exposed to the elevated plus maze, a test for anxiety or to one out of two different control conditions: i) unspecific stress induced by white noise (95 dB) or ii) presentation of food following a 10 hrs fasting period. Basal levels of glucose, determined using zero-net-flux, and the basal lactate/pyruvate ratio were 1.48+/-0.05 mmol/l and 13.8+/-1.1, respectively. In rats without manipulation glucose levels remained constant throughout the experiment (120 min). Exposure to the elevated plus maze, however, led to a temporary decline in hippocampal glucose (-33.2+/-4.4%) which reverted to baseline within 10 minutes after return to the familiar home cage. White noise decreased extracellular glucose level (-9.3+/-3.5%) non-significantly. In hungry rats, immediately after presentation of food, a significant reversible drop in hippocampal glucose levels (-19.7+/-5.9%) was determined for about 10 minutes. In all groups, the lactate/pyruvate ratio remained unchanged by the experimental procedures. Our microdialysis study demonstrates that exposure to the elevated plus maze, but also to food induces a transient decrease in extracellular hippocampal glucose concentration. In contrast, an unspecific stimulus did not change hippocampal glucose. The latter suggests that only specific behavioural stimuli increase hippocampal glucose utilization in the ventral hippocampus.

86 METABOLIC CONSEQUENCES OF CAVEOLIN 3 MUTATIONS

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Objectives: Caveolae are small invaginations of the cell membrane important in compartmentalization

of signal transduction pathways. In neurons, all isoforms of caveolin are expressed and appear to be involved in regulation of neurotrophin signal transduction, neurite sprouting and synaptogenesis. In skeletal muscle, only caveolin 3 is found. Mutations in caveolin 3 (*CAV3*) lead to a variety of muscle disorders, including limb girdle muscular dystrophy1C, rippling muscle disease and hyperCKemia. Apart from fixed weakness the patients complain of lack of endurance and myalgias. *Cav3*-knockout mice have impaired glucose resistance. We asked whether skeletal muscle of patients with *CAV3* mutations may be functionally altered in terms of glucose utilisation. Methods: Six probands with defined *CAV3* mutations and ten controls were examined. A metabolic profile was obtained from all probands under resting conditions and during exercise. This consisted of glucose and fatty acids metabolites during an oral glucose tolerance test (ogtt) while microdialysis of skeletal muscle and adipose tissue was performed. Functional MR-imaging of skeletal muscle included ^{13}P, ^{23}Na, ^{1}H and whole-body-MRI. In addition, glucose uptake was measured in vitro in primary myoblast cultures from probands with *CAV3* mutations and controls.
Results: In vivo, in *CAV3*-deficient skeletal muscle we found significantly decreased glucose uptake during ogtt than in controls. Lactate was significantly elevated, whereas pyruvate, the metabolite of the anaerobic glucose oxidation, was significantly decreased. Blood flow as determined by ethanol ratio was reduced in diseased muscle. These findings were specific for skeletal muscle and were not seen in adipose tissue. In MR-imaging, the 1H-spectra of *CAV3*-deficient skeletal muscle detected only the intracellular lipid compartment while they failed to demonstrate extramyocellular lipids. *In vitro* myoblast studies are in progress.

87 EFFECTS OF UNCERTAINTY ON PERFORMANCE MONITORING IN OLDER ADULTS

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Event-related brain potential (ERP) studies identified the error related negativity (ERN/N_e) and the correct related negativity (CRN) to be related to performance monitoring. It has been repeatedly found that ERN/N_e amplitudes are attenuated in older compared with younger adults. Our previous research also showed age-related alteration in correct trials: the CRN amplitude was enhanced in older participants. A pattern of reduced ERN/N_e and enhanced CRN amplitudes has been associated with high decision uncertainty. The present experiment aimed to investigate whether age differences in ERN/N_e and CRN amplitudes are related to higher task uncertainty in older adults. Participants performed a visual discrimination task with four difficulty levels (very easy, easy, difficult, very difficult) to examine decision uncertainty while recording event-related potentials. They were asked to discriminate the size of two dots and to decide which one of these dots was larger. Subsequent response accuracy ratings (correct, incorrect or uncertain) allowed us to compare aware and unaware correct and incorrect reactions as well as trials classified as uncertain. ERN/N_e and CRN amplitudes were reduced in older compared to younger adults. Both groups showed attenuated ERN/N_e amplitudes with higher task difficulty. While in younger adults CRN amplitudes increased with higher task difficulty the CRN did not change in older adults. The percentage of uncertainty ratings did not depend on age. Further the distribution of uncertainty ratings corresponded not to the course of the CRN in the different task conditions. Whereas ERN/N_e amplitudes were attenuated with higher task difficulty in both age groups, only younger adults also showed a variation of CRN amplitudes. Thus, the present results indicate that age effects of ERN/Ne and CRN amplitudes seem not (only) to be due to decision uncertainty.

88 NOW YOU'LL FEEL IT – NOW YOU WON'T: PRE-STIMULUS EEG CORRELATES OF CONSCIOUS PERCEPTION

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A multitude of environmental events impinge on the receptor surfaces of our senses, yet only a minor fraction of them is perceived consciously. If several stimuli arrive at our sensors concomitantly, competing for an access to conscious perception, we cannot build a conscious percept of many even supra-threshold stimuli embedded in a context of more salient stimuli (masking). This raises intriguing questions about where and how in our brains the perceptual fate of a particular stimulus is determined. Using the high temporal resolution of EEG, we investigated the neuronal mechanism preceding conscious perception of supra-threshold somatosensory stimuli at the left index finger followed by stimuli of higher intensity at the right index finger (backward masking). The detection rate for the left index finger stimuli declined from 75 % when presented alone to 32 % when followed by a masking

stimulus. We identified two EEG signatures predictive for the access to somatosensory awareness: (i) 500 ms preceding an consciously perceived stimulus the left frontal cortex becomes active as indexed by regional beta rhythm (~ 20 Hz) desynchronization, (ii) an attenuation of mu (~ 10 Hz) and beta ‚idling' rhythms is found at those pericentral sensorimotor cortices that are going to process the upcoming target stimulus. Furthermore, the individual level of pre-stimulus mu- and beta band amplitudes over the frontal and somatosensory cortex is crucial for the proportion of perceived stimuli in a masking context. We suggest an activation of left frontal areas involved in top-down attentional control critical for screening against backward masking that leads the preparation of primary sensory cortices: The ensuing suppression of sensory idling rhythms may provoke a stronger neuronal response to the upcoming stimulus and therewith effectively promotes conscious perception of supra-threshold stimuli embedded into an ecologically relevant condition featuring competing environmental stimuli.

89 PERFORMANCE MONITORING AND DECISION-MAKING IN PATIENTS WITH BORDERLINE PERSONALITY DISORDER

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Marked impulsivity is considered to be a core characteristic of borderline personality disorder (BPD) and has been shown to play a significant role in decision-making and planning. In line with this notion, neuropsychological studies have found alterations in these executive functions which are related to dysfunctions of the prefrontal cortex in BPD. Despite the clinical relevance of decision-making in BPD, the number of studies investigating its neurophysiologic correlates is still small. In the present study, decision-making was examined in patients with BPD and matched healthy controls while performing a modified version of the Iowa Gambling Task (IGT) and an electroencephalogram was recorded. The IGT is a neuropsychological task designed to study mechanisms of diminished impulse control and risk-taking behaviour which relates to imbalanced activity between the prefrontal cortex and the amygdala. The clinical impression indicates that patients with BPD show alterations in negative feedback processing. Hence, an objective was to examine performance monitoring in patients with BPD by measuring the feedback negativity. The behavioural results suggest that patients with BPD showed less advantageous and more risky choices on the IGT than did the healthy controls. The ERP analysis indicated impairments in negative feedback processing in patients with BPD since feedback negativity was reduced. The attenuated feedback negativity reflects reduced action monitoring in patients with BPD and suggests dysfunctions of the ACC. In contrast, processing of outcome probability and value was not affected in BPD. However, since the study is not yet completed, the results are preliminary.

90 EXPRESSION OF A CALCIUM SENSOR PROTEIN IN MICROGLIA

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Microglial cells express a variety of neurotransmitter receptors. Activation of these receptors can lead to Ca^{2+} influx into the cytoplasm by release from internal stores or by opening channels in the cytoplasmic membrane. We have previously studied microglial Ca^{2+} signals in vitro using Ca-sensitive dyes, but so far Ca^{2+} signals in microglial cells in situ could not be analyzed since we (and others) have not found a procedure to load the cells with Ca^{2+} indicators. To overcome this restriction we have employed a Ca^{2+}-sensitive genetic construct G-CaMP2 [Tallini et al., PNAS. Vol. 103 (2006) 4753-58]. GCaMP2 is a fusion protein of GFP, calmoduline and a myosin chain. Ca^{2+}-dependent fluorescence changes result from the interaction between Ca^{2+}/calmodulin at the C terminus of circularly permuted GFP and an N-terminal myosin light chain kinase fragment. After transfection of primary microglia cells with the vector p-N1-G-CaMP2 using electroporation, we found GCaMP2 expression in more then 50% of cells. Moreover we can demonstrate that 48h after transfection, these microglial cells show an intracellular Ca^{2+} increase evoked by ATP application. When we added transfected microglia to an organotypical slice culture, we can also detect intracellular Ca^{2+} signals in response to ATP 48h after transfection. Since transfection of microglial cells by using electroporation is limited to cell culture, we created a retroviral vector expressing the calcium sensor protein G-CaMP2. By using this experimental approach, we could transfect cultured microglial cell with an efficiency of 35%. We were also able to transfect cells in organotypical slices. Our data show that the expression of the Ca^{2+} sensitive protein G-CaMP2 will be a useful tool for recording intracellular Ca^{2+} signals in microglial cells in situ.

91 IN VIVO IMAGING OF LYMPHOCYTES IN THE CNS REVEALS DYNAMIC T CELL COMPARTMENTALIZATION

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In the course of autoimmune CNS inflammation, inflammatory infiltrates form characteristic perivascular lymphocyte cuffs by mechanisms that are not yet well understood. Here, intravital two-photon imaging of the brain in anesthetized mice with experimental autoimmune encephalomyelitis (EAE) revealed the highly dynamic nature of perivascular immune cells, refuting suggestions that vessel cuffs are the result of a shortage of lymphocyte motility in the CNS. On the contrary, vessel-associated lymphocyte motility is an actively promoted mechanism which can be blocked by CXCR4 antagonism. In vivo blockade of CXCR4 in EAE disrupted dynamic vessel cuffs and resulted in invasive random migration. Furthermore, CXCR4-mediated perivascular lymphocyte movement along CNS vessels was a key feature of $CD4^+$ T cell subsets in contrast to motility in $CD8^+$ T cells, indicating a dominant role of the perivascular area primarily for $CD4^+$ T cells. We defined a new marker, the vector-vessel angle, which objectified this CNS specific behavior of $CD4^+$ T cells and reliably demarcated it from random migration as seen in $CD8^+$ T cells. Our results visualize dynamic T cell motility in the CNS in the living animal and demonstrate differential CXCR4-mediated compartmentalization of $CD4^+$ T cell motility within the healthy and diseased CNS.

92 A MOLECULAR DISSECTION OF TRPV1 SENSITISATION USING THE NAKED MOLE-RAT

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Tissue inflammation leads to pain and behavioral sensitization to thermal and mechanical stimuli called hyperalgesia. However, the African naked mole-rat (NMR, Heterocephalus glaber), has behavioral insensitivity to capsaicin and acid. Additionally, nerve growth factor (NGF) fails to induce thermal hyperalgesia, a phenomenon dependent upon TRPV1. We aimed to discover why NGF fails to induce thermal hyperalgesia in NMRs. In mouse the isolectin B4 (IB4) labels TrkA negative DRG cells and immunocytochemistry demonstrated the same pattern in NMR DRG cells. NGF sensitized the capsaicin-gated current in mouse DRG neurons that were IB4-ve (n = 11), but failed to do so in either IB4+ve or IB-ve NMR DRG neurons (n = 14). Cloned NMR TRPV1 possesses the Y200 residue that in other species is fundamental for NGF-induced sensitization in TRPV1. When expressed in CHO cells NMR TRPV1 is activated by heat, capsaicin, pH and voltage in a similar fashion to TRPV1s from other species. We introduced NMR TRPV1 into DRG neurons from $TRPV1^{-/-}$ mice and in this context NGF caused potentiation of NMR TRPV1 in IB4-ve neurons (n = 8). This data suggests that there is something about NMR cells or NMR TrkA that is responsible for the lack of sensitization observed. To determine if the cellular environment is critical for NGF induced sensitization, a new fibroblast cell line was established from NMR kidney tissue. Four clones were isolated and have reached population doublings in excess of 40. We are using these cells to test the hypothesis of whether the cellular environment of NMR cells is responsible for the lack of NGF induced sensitization. To conclude, NGF fails to sensitize NMR TRPV1, which may account for the lack of NGF-induced thermal hyperalgesia in NMRs. Evidence suggests that there is a difference in NMR TrkA or downstream signaling that underlies the lack of sensitization and these mechanisms are under investigation.

93 PLASTICITY-RELATED GENE-1 SIGNAL TRANSDUCTION

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Lysophosphatidate (LPA) is involved in controlling cell signaling including the regulation of cell division, death and movement. In vivo concentration of LPA in brain tissue ranges is measured in μM. Our analyses of LPA-effects on neurons show that LPA induces vesicle release on a subtype of synapses. LPA activates at least five G-protein-coupled receptors (LPA_{1-5}). Each receptor can couple with multiple types of G proteins ($G_{12/13}$, $G_{i/o}$, $G_{q/11}$, G_s) to activate a range of downstream pathways. We found that LPA induces effects on neurons by coupling to the LPA2 receptor, which leads to an intracellular calcium increase. Extracellular LPA levels are controlled by a variety of actors, including enzymes, namely three lipid phosphates phosphatases (LPPs), which degrade LPA to mono-acyl-glycerol and thus also regulate many aspects of signaling transductions. We identified a set of five brain-specifically expressed membrane proteins, which define a subclass of the LPP-superfamily, the plasticity related genes (PRGs), which, in the case of PRG-1, attenuate LPA-induced effects on synapses. Further, we were able to identify that PRG-1 interacts intracellularly with regulators of the Ras-Rac signaling pathway depending on the LPA level extracellular. This protein-protein interaction controls N-Ras activity. Ras proteins are known to be involved in the growth and development of tumor. Interestingly, PRG-1 expression was found to be elevated in human prostate cancer tissue.

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94 ANALYSES OF PRG-1/RAS GRF-2 INTERACTION AND SIGNALING EFFECTS

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Plasticity-related gene-1 (PRG-1) was the first member of the plasticity-related gene family (PRG-1-5) to be identified. PRGs belong to the lipid phosphate phosphatases (LPP) superfamily whose members have an extracellular ectoenzymatic activity, which is able to dephosphorylate lysophosphatidic acid (LPA) into its inactive monomers. LPP-superfamily members are widely expressed, but PRG-1 is brain-specific; PRG-1 expression in vivo increases after birth, is still detectable in adult mouse brain and is upregulated after brain lesion. Interestingly, PRG-1 has a particularly large intracellular C-terminus (400 amino acids). To identify the pathway involved in PRG-1, a yeast two-hybrid screening was performed. One of the putative interaction partners found was Ras-specific exchange factor 2 (Ras GRF-2). Ras GRF-2 belongs to a family of calcium/calmodulin-regulated guanine nucleotide exchange factors that activates Ras proteins. We could confirm the following: first, expression of PRG-1 and Ras GRF-2 during brain development; second, colocalization of PRG-1 and Ras GRF-2 in primary neurons; third, the interaction between both proteins after overexpression in mammalian cells, as well as endogenously in primary neurons using co-immunoprecipitation assays; Fourth, modification of PRG-1/Ras GRF-2 interaction after extracellular induction using LPA; and fifth, the direct effect of PRG-1/Ras GRF-2 interaction on N-Ras inactivation. In summary, the results lead us to speculate a putative role for PRG-1 as a Ras-cascade controller. Further studies are being conducted to confirm this, not only to map the interaction (using several PRG-1 C-terminus-deleted mutants), but also to understand its signaling.

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95 OPIOID WITHDRAWAL INCREASES TRPV1 ACTIVITY IN A PKA DEPENDENT MANNER

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Vanilloid receptor type 1 (TRPV1) is a ligand-gated ion channel expressed on sensory nerves that responds to noxious heat, protons, and chemical stimuli such as capsaicin. TRPV1 plays a critical role in the development of tissue injury, inflammation or nerve lesions. Opioids such as morphine have been used widely for the treatment of many types of acute and chronic pain. Application of morphine leads to a dissociation of G-proteins and causes a reduced activity of adenylylcyclases (AC), resulting in a lower amount of cAMP. However, opioid withdrawal following chronic activation of the μ opioid receptor induces AC superactivation and subsequently an increase in cAMP and Protein Kinase A (PKA) activity. In the current project we investigated wether an increase in cAMP during opioid withdrawal increases the activity of TRPV1. In whole cell patch clamp and calcium imaging experiments opioids significantly increase capsaicin induced TRPV1 activity in a nalaxone and pertussis toxin sensitive manner. The role of different PKA phosphorylation sites at TRPV1 was investigated using site-directed mutagenesis. In summery, our results demonstrate that opioid withdrawal can increase the activity of TRPV1. These observations show a new mechanism underlying hyperalgesia during opioid withdrawal.

96 INTERFERON-ß REVERSIBLY ATTENUATES I_h IN ADULT NEOCOR-TICAL PYRAMIDAL NEURONS IN VITRO

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The cytokine IFN-ß modulates neuronal function by increasing the excitability of neurons: it reversibly influenced the subthreshold membrane response by raising the membrane resistance R_M 2.5-fold and the membrane time constant t1.7-fold dose-dependently. The effect required permanent exposure to IFN-ß and was reduced in magnitude if the extracellular K^+ was lowered. However, the membrane response to IFN- ß in the subthreshold range was prevented by ZD7288 (a specific blocker of I_h) but not by Ni^{2+}, carbachol, or bicuculline, pointing to a dependence on an intact I_h. Consequently we directly showed by in vitro whole cell patch clamp recordings of layer V pyramidal neurons in the somatosensory cortex of adult rats that IFN-ß markedly and reversibly reduced the current carried by hyperpolarization-activated cyclic nucleotide gated (HCN) channels, namely the slow I_h and the instantaneous I_{inst}. In case of I_h, IFN-ß appeared to predominantly affect the fastest current component as indicated by a concomitant 1.2-fold increase of the first but not the second time constant of activation. All IFN-ß effects were dose dependent with an IC_{50} of ~900 IU. Preliminary data point to a Type 1 IFN-α/ß receptor mediated effect because blockade of the IFN1-receptor induced JAK1/Tyk2 activation by JAK1 inhibitor prevented IFN-ß effects almost completely. On the contrary a preferential blockade of JAK2 by AG490 did not interfere with the IFN-ß induced I_h reduction. The data suggest that IFN-ß can directly influence the membrane properties

of layer V neocortical neurons by receptor mediated modulation of HCN channel activity. This action may underlie some of the effects of IFN-ß on brain function.

97 THE CONSOLIDATION OF AN EXTINCTION MEMORY DEPENDS ON THE MAGNITUDE OF THE PREDICTION ERROR DURING MEMORY RETRIEVAL

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In classical conditioning an animal learns that a previous neutral stimulus (conditioned stimulus, CS) acts as a predictor for the appearance of a biologically significant stimulus (unconditioned stimulus, US). After an association has formed animals display the conditioned response (CR) in anticipation of the US. Retrieving a consolidated memory about a CS-US association with an unreinforced CS-presentation results in two contrasting memories. One is formed about the fact that the CS is no longer predicted by the US. This memory is termed extinction memory. The second is formed about the previously learned CS-US association, a process termed reconsolidation. The mechanisms underlying these consolidation processes after retrieval are still unclear. One critical factor for the induction of one or the other consolidation process is the intensity of the training. According to the Rescorla-Wagner-Model the associative strength of a CS increases with every training trial until it reaches a maximum. Thus, the associative strength of the CS appears to be critical for memory consolidation after retrieval. In this study, we tested this prediction in an pavlovian, appetitive learning paradigm in the honeybee (Apis mellifera). We varied the length of US presentation, which is proposed to be directly related to the associative strength. Associative strength is thought to be reflected during acquisition by its effects on the animal's CRs. In the present study US length, showed no effect on the animals CRs during acquisition. Moreover, when bees trained with different US duration were exposed to CS presentations 24 h later no differences in their CRs were observed. However, a consolidation blocker applied prior to the presentation of CS-only trials revealed that the duration of the last US presentation during training is critical for a consolidation process to occur after memory retrieval. We conclude from this that it is the magnitude of the prediction error during memory retrieval that affects memory consolidation after retrieval.

98 ANALYSIS OF PHOSPHORYLATION TARGETS OF THE CGKI IN DEVELOPING DORSAL ROOT GANGLIA WHICH ARE IMPORTANT FOR AXON BIFURCATION IN THE SPINAL CORD

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Our lab showed that cGMP signaling via cGMP dependent protein kinase I (cGKI) is important in axonal pathfinding and connectivity of sensory neurons in vivo. Sensory axons bifurcate upon arrival at the dorsal root entry zone (DREZ) of the spinal cord and grow further in both rostral and caudal directions. However, sensory axons of mice lacking cGKI do not bifurcate, they turn instead and grow in either caudal or rostral direction. These initial studies raised the question which other components are part of the cGMP signaling cascade in sensory axons. PCR-screen of guanylyl cyclase expression carried out in our lab indicated that natriuretic peptide receptor 2 (Npr2) might be responsible for cGMP production in dorsal root ganglia. When we studied afferent sensory projections in embryonic mice which lack functional Npr2 we observed the same axonal bifurcation errors as in cGKI knock-out mice. Our data suggest that cGMP signaling via Npr2 and cGKI is important for axon bifurcation at the DREZ. However, downstream phosphorylation targets of cGKI involved in axon bifurcation remain to be identified. We are searching for downstream components of the cGMP signaling cascade in sensory axons by analysing mice deficient for established phosphorylation substrates of cGKI. In addition, we screen for novel phosphorylation targets of cGKI using an antibody recognizing a phosphorylation consensus motif of cGKI. Experiments carried out so far let us exclude Mena and VASP proteins as candidate-proteins that could play a role in axon bifurcation. Western blots with the phospho-sequence specific antibody revealed several proteins that become phosphorylated upon stimulation of cGKI in dorsal root ganglia or in a cell line derived from dorsal root ganglia. Currently we focus on two components to enrich these for mass spectrometry analysis.

99 PERINATAL HYPERPOLARIZATION-ACTIVATED CHANNEL SUBTYPE REARRANGEMENT IN NEOCORTICAL PYRAMIDAL NEURONS

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HCN channels - that conduct the hyperpolarization activated current I_h - play a paramount role in stabilizing resting membrane potential and controlling cell

excitability in adulthood and during postnatal development. We have discovered profound changes in HCN subunit expression around the time of birth which were partially transcriptional regulated. The early, strong expression of the ‚slow' subunits HCN3 and HCN4 with a rapid decline postnatally appears to be particularly important, shedding light on their role in cortical development. In contrast, HCN1 and HCN2 expeditiously increased postnatally. The distinct pattern of HCN subunit expression was reflected in I_h properties which were changed in two kinetically distinct manners. Firstly, a rapid change characterized by a shift in voltage sensitivity to hyperpolarized values and by an accelerated deactivation occurred within postnatal day 1. Secondly, an 7-fold increase in current density accompanied by a diminution of activation kinetics and a shift in reversal potential emerged in about 35 postnatal days. These findings point to a new role for HCN3 and adds evidence to the suspected impact of HCN4 in neuronal development.

100 PAIN ATTENUATION IN TETHERED-TOXIN TRANSGENIC MICE DUE TO REDUCED EXCITABILITY OF SENSORY NEURONS

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Toxins derived from venomous animals have been widely employed in neuroscience research because of their ability to modulate specific ion channels. Our group has developed a new strategy using peptide toxins that are tethered to the membrane via a GPI anchor and retain their specific action on ion channel subtypes while acting in a cell-autonomous manner. Since alterations in the function of voltage gated sodium channels (VGSCs) lead to hyperexcitability that causes chronic pain, we wanted to use this strategy to specifically manipulate these channels in vivo. We generated transgenic mice using the bacterial artificial chromosome (BAC) of the Nav1.8 VGSC to drive expression of the MrVIA conotoxin. This toxin is a potent blocker of this tetrodoxin resistant (TTX-R) channel, which plays a major role in nociception. A significant reduction of VGSC currents in nociceptive neurons was observed while mechanoreceptors where not affected, demonstrating the cell subtype specificity of this approach. This block was restricted to TTX-R currents and not compensated by upregulation of TTX-S currents as was observed in Nav1.8 knockout mice (Akopian et al). The Nav1.8 gene is predominantly expressed in non-peptidergic nociceptors (IB4+) and consistent with this we observed an enhanced block in this cell subpopulation. Behavioral studies revealed a remarkable lower sensitivity to noxious cold stimuli in the transgenic toxin mice. Thus these studies provide the first proof of function of the BAC transgenic tethered toxin approach in mammals and its suitability for developing new therapeutic mouse models for pain research.

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101 ROLE OF PRG-1 IN HIPPOCAMPAL EXCITABILITY

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The information transmission at synapses is essential for neuronal processing in the nervous system. Abnormal excitation can lead to seizures in form of epilepsy. We identified PRG-1, a member of the Lipid Phosphate Phosphatase (LPP) superfamily, as a critical mediator of excitation at glutamatergic synapses. PRG-1 is brain specific, and is expressed exclusively in glutamatergic neurons and not in glial cells. In heterozygous breeding around 50% of PRG-1 null mice die before P21 due to epileptic seizures. We confirmed this phenotype by in-vivo EEG recordings of PRG-1 deficient mice which showed tonic-clonic seizures starting at P20. Field recordings in area CA1 of hippocampus slices showed significantly increased excitability in PRG-1 deficient mice and heterozygous mice. In single cell recordings of pyramidal neurons of the CA1 area, the frequency of miniature EPSCs was significantly increased in the knock-out mouse at P21. However, the intrinsic properties like action potential amplitude or resting membrane potential of CA1 pyramidal neurons showed no differences between PRG1 deficient and wild type cells. Expression of postsynaptic receptors and vesicular GABA or Glutamate transporters was not altered in the KO-Mice. In adult KO-mice typical anatomical alterations such as mossy fiber sprouting and hippocampal sclerosis caused by epilepsy were observed. Thus, our findings reveal a novel mechanism that exerts important modulatory control of glutamatergic transmission and hippocampal excitability.

102 THE INVOLVEMENT OF LIPID PHOSPHATE PHOSPHATASES IN CORTICOGENESIS

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Lipid phosphate phosphatases (LPP) are integral membrane proteins, which comprise six transmembrane domains. To date, three LPPs (LPP-1–3) and a splice variant (LPP-1a) have been identified. They are known to act as ectoenzymes, able to dephosphorylate and thereby control the levels of extracellular phospholipids such as lysophosphatidic acid (LPA) and phosphatidic acid (PA). LPA is an extracellular lipid mediator with a wide variety of biological actions, including, in particular, induction of cell proliferation, migration and survival. It is known that the overexpression of LPP-1 shapes the LPA-induced migration of fibroblasts in wound-healing assays *in vitro*. However, their expression, distribution and function in the brain remain unclear. In this study we were able to show by means of real time PCR that LPP-1 mRNA is only weakly expressed in the neocortex, whereas LPP-1a expression is approximately ten times stronger. Both genes are expressed throughout embryonic and postnatal development. We created an RNAi construct that specifically downregulates both splice variants. In vivo analysis of LPP-1 and LPP-1a knock down during development by in utero electroporation showed that LPP-1 and/or LPP-1a play an important role in corticogenesis. Cortical neurons that lack LPP-1 and LPP-1a expression are no longer able to migrate to their proper layer. Further analysis of electroporated neurons also showed possible alterations in dendritic tree morphology. Our data provide evidence to suggest that the expression level of lipid modulators such as LPP-1 and LPP-1a and their control of the bioactive LPA-levels are important for neuronal migration, cortical layer formation and perhaps differentiation in early embryonic neocortex development.

103 LOWER MOTOR NEURON LOSS: MULTIPLE SCLEROSIS AS - A NEURODEGENERATIVE DISEASE?

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Classical textbooks characterize multiple sclerosis (MS) as a chronic inflammatory and demyelinating disease of the CNS, but neither neurodegeneration nor lower motor neuron loss are stated as typical features of MS. Nerve conduction studies showed significantly lower compound muscle action potentials and a significantly lower number of motor neurons in MS patients versus controls, suggesting that spinal motor neurons were affected. To determine whether neuronal cell loss occurs in neuroinflammation, we assessed absolute numbers of neurons using high-precision, design-based stereology in patients with MS, but also in experimental autoimmune encephalomyelitis (EAE), the animal model of MS. Surprisingly, we found a substantial loss of lower motor neurons in MS patients (54 $\pm$ 18%), although this was not observed to this extent in cortical neurons. Lower motor neuron loss was also found in different EAE models (49 $\pm$ 11% to 76 $\pm$ 8%) but was abolished in EAE induced with TRAIL -/- T cells. Our study reveals damage to the lower motor neuron as a significant feature, and neurodegeneration as a major hallmark of MS.

104 ACUTE ALBUMIN EXPOSURE EFFECTS ARE STIMULATION FREQUENCY DEPENDENT AND SUGGEST POTASSIUM BUFFERING IMPAIRMENT

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The majority of insults that potentially lead to the development of chronic secondary epilepsy manifest through a temporary loss of integrity of the blood brain barrier (BBB), and subsequent infiltration of plasma-specific proteins into the cerebral spinal fluid. Recent results point to serum albumin as a main cause of astrocytic activation characterized by down regulation of Kir4.1 channels and changes in expression of glutamate transporters. Modeling work predicted that induction of epileptiform discharges is facilitated due to alterations in potassium (K^+) clearance when low frequency stimulation is used, while decline in glutamate transport would favor generation of epileptiform discharges if high frequency stimulation were used. We used horizontal slices to test for effects of albumin on neuronal activity while recording in somatosensory, temporal and entorhinal cortex. Acute albumin exposure led after a few hours to the appearance of abnormal field potential responses in cortical layer IV and II, for layer VI stimulation, in all studied regions. The effects of albumin were measured in presence and absence of 2mM glutamine. Spontaneous epileptiform events appeared only in the presence of glutamine in entorhinal cortex and temporal neocortex, where albumin is preferentially taken up during a generalized

exposure. Additionally, repetitive stimulation with different frequencies could induce epileptiform afterdischarges. Low frequency stimulation was more successful than high frequency stimulation. This result is compatible with modeling work indicating that impairment of spatial K^+ buffering and abnormal K^+ accumulation is involved in generating abnormal discharges after low frequency stimulation.
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105 THE ROLE OF THE THYROID HORMONE-SPECIFIC TRANSPORTER MCT8 IN CNS DEVELOPMENT

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Thyroid hormones are essential for the proper development of a variety of tissues, especially the nervous system. Their transport into target cells is mediated by thyroid hormone transporters like the monocarboxylate transporter 8. Mutations in this X-chromosomal gene in humans lead to a severe phenotype with lack of mental development after birth, derangement of thyroid hormone levels including high T3 and low T4, with no significant changes in TSH. Interestingly, despite high T3 the patients do not show tachycardia. Here we present data on the expression of MCT8 in various tissues in human and mouse. Despite the lack of the same obvious phenotype in the MCT8 knock-out mouse, the transporter causes reduced anxiety-related behaviour and hyperalgesia in these mice. Thyroid hormone transport is significantly down-regulated in MCT8-deficient primary cortical neurons. We could find an up-regulation of other thyroid hormone transporters in these cells from KO mice which could account for the incomplete loss of thyroid hormone uptake in these cells.

106 RGS PROTEIN SUPPRESSION OF G ALPHA(O) PROTEIN-MEDIATED ALPHA-2A ADRENERGIC INHIBITION OF MOUSE HIPPOCAMPAL CA3 EPILEPTIFORM ACTIVITY

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G-protein coupled α_2 adrenergic receptor (AR) activation by epinephrine (EPI) inhibits epileptiform activity in the mouse hippocampal CA3 region. The mechanism underlying this action is unclear. This study investigated which subtypes of α_2ARs and G-proteins ($G\alpha_s$ or $G\alpha_{i_1}$) were involved in this response using recordings of CA3 epileptiform bursts in mouse brain slices. First, we determined that this effect was mediated by the 2AAR subtype as the inhibitory action of EPI on burst frequency was abolished in slices from α_{2A}AR, but not α_{2C}AR, knockout mice. Next, using transgenic mice with the G184S Gnai2 allele (knock-ins) which prevents inhibition by interruption of the G-protein alpha subunit binding to regulators of G-protein signaling (RGS), we found enhanced α_{2A}AR effects in hippocampal slices from mutant $G\alpha_o$ mice but not $G\alpha_{i_2}$ mice. These results indicate that the EPI-mediated inhibition of mouse hippocampal CA3 epileptiform activity is through an α_{2A}AR $G\alpha_o$ mediated pathway under inhibitory control by RGS proteins. This suggests a role for RGS inhibitors as a novel antiepileptic drug therapy. Supported by American Physiological Society, ND EPSCoR EPS-0447679, NSF 0347259, NSF 0639227, NIH P20RR0167141, NIH 5RO1DA 17963 and NIH 5RO1GM039561.

107 PERIPHERAL AND CENTRAL ORGANIZATION OF THE LATERAL LINE PATHWAY IN XENOPUS LAEVIS

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Aquatic vertebrates like *Xenopus* make use of a lateral line (LL) system to detect water surface waves elicited by prey or predator movements. In *Xenopus*, only a few neuroanatomical studies on the LL-pathway exist, and the assignment of CNS nuclei to different LL-processing tasks remains incomplete. In a first step, the spatial arrangement of primary afferents into the CNS from individual peripheral LL-organs was investigated by a newly established double-labelling procedure using different tracers (neurobiotin and HRP). In the CNS, a combined neurophysiological and neuroanatomical approach was used for labelling experiments: responses of LL units were extracellularly recorded in different regions of the midbrain of *Xenopus*. Subsequently, neurobiotin was iontophoretically applied to reconstruct recording sites, and to track tracer transport. Injections were applied in the optic tectum (OT; 7 animals), as well as the principal nucleus of torus semicircularis (TP; 2 animals). In all animals and both injection sites, strong ipsilateral retrograde labelling of cell bodies in three tegmental subdivisions (dorsal, ventral, and

nucleus isthmi) was observed ($N_{OT\text{-}Injection}$=25; $N_{TP\text{-}Injection}$=18; mean). In 5 of 9 frogs, significant ipsilateral retrograde transport was observed in the laminar nucleus of torus semicircularis after injection in the OT and the TP (N_{OT}=19 (mean); N_{TP}=15). Other than OT injections, both TP injections demonstrate significant ascending input from decussating LL-fibres coming from the lateral line nucleus of the medulla (N_{MED}=10, and 31 respectively). Both the OT and the TP receive descending fibres from diencephalic nuclei indicated by retrogradely filled cell bodies (N_{TP}=15; N_{OT}=9; mean). The results suggest the tegmentum and the laminar torus participate in LL-processing, and confirm that the TP is a main projection area of medullary LL-neurones. Descending projections from the diencephalon might indicate efferent control from higher levels in the LL-hierarchy.

108 HYPERPHOSPHORYLATION OF TAU IN NPC-/- P301L-TAU+/+ MICE

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Neurofibrillary Tangles (NFTs), intracellular deposits consisting mostly of insoluble microtubule-associated protein tau, are a hallmark for a wide range of neurodegenerative diseases including Alzheimer's disease, frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17) and Niemann-Pick-disease type C (NPC). A number of animal models has been created to mimick these diseases. But while much has been learned by investigating these models, the specific mechanisms leading to the formation of NFTs are still unclear. While NFTs can be found in P301L-tau-mice older than 3 months, npc-mice do not develop NFTs. By creating a new mouse model by crossing balb/c npc-mice with P301L-tau-mice we sought to find out if NPC-disease could increase or accelerate tau pathology in mice posessing human tau with P301L-mutation. Comparing npc-/- P301L-tau+/+ with npc+/+ P301L-tau+/+ mice, we found in npc-/- P301L-tau+/+ mice an increase of tau phosphorylated at some epitopes (AT8, AT180), but an decrease of tau phosphorylated at the 12E8 epitope and no increase of the amount of tau phosphorylated at the AT100 epitope or in the number of NFTs. Although tau phosphorylation is thought a necessary prerequisite for NFT formation, we did not find more NFTs in spite of tau hyperphosphorylation at some epitopes. So further investigations are needed to understand the chain of events that lead from hyperphosphorylated tau to NFTs formation.

109 ROLE OF THE FOXP2 GENE IN PROLIFERATION AND NEUROGENESIS IN THE VENTRICULAR ZONE OF ZEBRA FINCHES, AN AREA DELIVERING NEWLY BORN NEURONS TO THE SONG NUCLEI AREA X

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So far it is known that FoxP2, a member of the forkhead box transcription factors, is involved in learning and acquisition of speech and song in humans and songbirds like zebra finches, respectively. In the male zebra finch it is, amongst others, expressed in the ventricular zone, the region where new neurons arise, and in two song nuclei, HVC in the pallium and Area X in the striatum, whereto a part of the newly born neurons of the ventricular zone migrate during the sensorimotory learning phase. To test if the FoxP2 gene may have a main function in regulating neurogenesis and in predefining the morphologic structures of the newly born neurons, I perform knock-down experiments in the ventricular zone via stereotactical injections of a self-made lentivirus, and analyse potential changes in the total amount and in the structure of new cells. To make the changes visible, I perform immunohistochemistry with antibodies against GFP, which is expressed by the virus, against BrdU, which is a thymidin-analogon that is incorporated into the DNA of dividing cells and which I apply one week after the virus injections, and against Hu, a general marker of neurons.

110 FOXP2 TARGET GENES IN AREA X OF ZEBRA FINCHES

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Mutations of the transcription factor FoxP2 are causing Developmental Verbal Dyspraxia (DVD), a disorder where the affected individuals show severe impairments in the expression and reception of speech and language. Studies have shown that FoxP2 is differentially expressed in a nucleus of the avian basal ganglia, namely Area X, during the period where the bird learns its song. A knockdown of FoxP2 in Area X during that sensitive phase leads to the incomplete and inaccurate acquisition of the tutor song. As FoxP2 is a transcription factor the displayed phenotype is likely due to the missregulation of its downstream target genes. Therefore the identification and further investigation of those targets will lead to a better understanding of the role of FoxP2 in learning. In my diploma thesis I am validating ChIP-on-Chip predicted FoxP2 targets by doing in situ hybridizations on zebra finch brains of different ages, with and without FoxP2 knockdown. Targets that are

differentially expressed in Area X and colocalize with FoxP2 will be further investigated in in vivo knockdown experiments, that will allow us to enlighten the role of FoxP2 and its target genes in auditory guided motor learning.

SFB 507 "Role of non-neuronal cells in neurological disorders"

The Sonderforschungsbereich 507 was funded from 1995 to 2007 and investigated the role of non-neuronal cells in CNS disease. In particular, the role of astrocytes, microglia, and endothelial cells in neurological diseases such as stroke, multiple sclerosis, meningitis, and epilepsy was studied. Systems-physiological, molecular, and cellular strategies were utilized to understand the complex interaction of neurons and non-neuronal cells in models of neurological disorders. Special emphasis was put on clinical relevance, since it was the ultimate goal of this collaborative effort, which briought together clinical departments with basic research units, to develop new diagnostic and therapeutic tools. The SFB 507 was coordinated by Ulrich Dirnagl (‚Sprecher', Charité Exp. Neurology), Uwe Heinemann (Charité Physiology), Frauke Zipp (Charité Neuroimmunology), Helmut Kettenmann (MDC), and Jens Dreier (Charité Neurology).

Projektbereich A
A1 ‚Cortical spreading ischemia', Dreier/Einhäupl
A5 Rekrutierung myeloider und lymphoider Zellen ins ZNS nach experimentellem Schlaganfall, Priller/Dirnagl
A9 Angiogenese und Vaskulogenese nach milder zerebraler Ischämie, Endres
Projektbereich B
B6 Zelluläre Schädigung der Blut-Hirn-Schranke - Ein Schlüsselmechanismus in der Schadenskaskade der bakteriellen Meningitis, Weber/Braun
B11 Die Rolle des Netzwerkes nicht-neuronaler Zellen bei axonalem Auswachsen, Nitsch/Müller-Röver
B14 Mechanismen der Immunzell-vermittelten Schädigung in der chronischen Entzündung des Zentralnervensystems, Zipp/Aktas
B16 Die Rolle der Mikroglia bei postläsionalen Veränderungen in Schichten anterograder axonaler Läsion, Bechmann
B18 Das Proteasom in Mikroglia und Astrozyten und seine Rolle bei Infektions- und Entzündungsprozessen im ZNS, Kloetzel/Dahlmann
Projektbereich C
C3 Funktionen von Gliazellen während epileptogener Prozesse, Heinemann/Kann
C7 In situ Untersuchungen zu physiologischen Mechanismen der Mikrogliaaktivierung unter pathophysiologischen Bedingungen, Schilling/Eder
C10 Kommunikation von Mikrogliazellen mit Astrozyten und Neuronen, Kettenmann
C12 Die Bedeutung von Bluthirnschrankenstörungen für Dysfunktionen des cerebralen Cortex, Friedman/Heinemann

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SFB 665 "Entwicklungsstörungen im Nervensystem" („Developmental Disturbances in the Nervous System")

Seit Juli 2005 fördert die Deutsche Forschungsgemeinschaft (DFG) den Sonderforschungsbereich 665 »Developmental Disturbances in the Nervous System«, der von der Charité geleitet wird. 15 Forscherteams aus der Charité – Universitätsmedizin Berlin, der gemeinsamen Einrichtung der Freien Universität (FU), der Humboldt- Universität zu Berlin (HU), dem Max-Delbrück-Centrum für Molekulare Medizin (MDC) und dem Institut für Biologie der FU, forschen zusammen nach Wegen, Entwicklungsstörungen des Nervensystems aufzuklären.

Wie das Nervensystem während der Entwicklung ausgebildet wird, ist ausschlaggebend für seine spätere Funktion. Fortschritte in der Genetik und der Molekularbiologie in den letzten zwei Jahrzehnten haben es ermöglicht, Moleküle zu analysieren, welche die Entwicklung des zentralen Nervensystems steuern, und genetische Veränderungen zu identifizieren, die zu einer Störung dieses Prozesses führen. Wenn beispielsweise durch eine Mutationen kritische Zellfunktionen gestört sind, führt dies oft zu einer Kaskade weiterer Probleme, die schließlich zu einer Anzahl klinischer Syndrome führen können, wie z.B. Schwerhörigkeit, Epilepsie oder Sprachstörungen.

Wie neuronale Schaltungen gebildet und aufrechterhalten werden, ist jedoch bis jetzt nur teilweise aufgeklärt. Die Herausforderung für Grundlagenforscher und klinische Neurowissenschaftler ist deshalb, das Wissen über molekulare Mechanismen, welches durch Tiermodelle gewonnen wurde, in das Verständnis von Entwicklungsstörungen bei Patienten zu integrieren. Langfristiges Ziel des SFB 665 ist es deshalb, Kausalzusammenhänge zwischen Mutationen und neurologischen Phänotypen aufzuklären und dadurch eine Basis für zukünftige Verbesserungen therapeutischer Strategien zu schaffen. Der SFB 665 stellt sich diesen Herausforderungen, indem er Grundlagenforscher und Kliniker zusammenbringt, um die Funktionen des Nervensystems auf zellulären, biochemischen oder physiologischen Ebenen zu untersuchen und die genetischen Ursachen von Entwicklungsstörungen bei Patienten zu identifizieren.

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SFB/TRR 43 "The Brain as a Target of Inflammatory Processes"

Recent paradigm shifts in our understanding of pathologies of the central nervous system (CNS) call for elucidation of the underlying molecular processes. It has become evident that classical inflammatory disorders of the CNS such as multiple sclerosis and meningitis target the neuroaxonal compartment, an aspect which has been neglected for over a century. Moreover, evidence is growing for a fundamental role of both innate and adaptive immunity in pathologies which have not hitherto been regarded as inflammatory, such as stroke – both ischemic and hemorrhagic – and axonal/neuronal injury due to traumatic or degenerative causes.
In this SFB, researchers from Berlin and Göttingen have come together to take up the challenges of this emerging field, by combining the efforts of clinicians and basic scientists, neuroimmunologists and neurobiologists. The key questions we seek to answer are as follows:
• Under what circumstances and by what mechanisms do immune cells enter the CNS and interact with, or even attack, local neural cells?
• Does the involvement of the immune system in different pathologies result in additional damage or does it, in specific situations, promote repair, and if so, what are the molecular processes of immune-mediated damage and repair within the CNS?
Two features of the interaction of the immune system with the nervous system form the organizational basis of our SFB: firstly, the rapid innate immune (i.e. microglial) responses, with microglia being part of both the immune and the nervous system (project area A); secondly, adaptive immune (i.e. T cell) responses, since T cells infiltrate and traffic through the CNS in various CNS diseases (project area B). It is our hypothesis that the crosstalk of the nervous and immune systems is a common mechanism in various pathological conditions, and as such a suitable target for therapeutic interventions.

Speaker: Prof. Dr. Frauke Zipp

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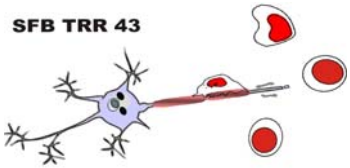

Final Colloquium of the SFB 507

GRK 429 "Doctoral Program on Neuropsychiatry and Psychology of Aging"

Central Themes of the Program:
It is generally agreed that, in order to understand the many aspects of old age and aging, it is important to strive for a transdisciplinary perspective and systematic integration. To this end, two main goals of the Research Training Program on the neuropsychiatry and psychology of aging are:

- To integrate neuropsychiatric and psychological questions in research on aging
- To focus on issues of healthy and pathological aging.

In addition, the program seeks to integrate gerontological research and themes with studies and theoretical frameworks from health psychology.

Several topics serve as a forum for these integrative efforts. These include: brain aging and plasticity, pathological versus normal aging, the gain-loss dynamics of aging, the potential and limits of old age, cognition and sleep in elderly persons, and the nature of resiliency in old age.

One of the main research project currently in progress is called, "Berlin stays fit". It examines the effect of cognitively versus physically stimulating activities on the cognitive status of healthy elderly women.

Speaker: Prof. Dr. Isabella Heuser

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Neuropsychiatry and Psychology of Aging

GRK 1258 „Der Einfluss von Entzündungen auf die Funktion des Nervensystems“ („The impact of inflammation on nervous system function“)

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 trauma and ischemia, or even in functions of the nervous system, such as pain transmission. In all of these conditions or disorders, immune cells interact with cells of the nervous system. Although the initiating events differ considerably, we hypothesize common pathways in the crosstalk between immune and nervous system. The faculty of this graduate program studies this crosstalk by combining modern methods of molecular and cellular biology with imaging techniques (two photon microscopy, near-infrared fluorescence, and magnetic resonance imaging). We employ in vivo and in vitro approaches including animal models of neuroinflammation, ischemia, and arthritis, and in parallel we offer students experience in outpatient clinics and ward-rounds.

Our aim is to elucidate the influence of both proinflammatory and regulatory immune cells, via contact or soluble mediators, on brain cells, namely astrocytes, microglial cells and neurons. We will analyse the immune-triggered responses of brain cells and study their impact on function, pathologic processes, damage cascades, and regeneration in nervous tissue. Studying the underlying mechanisms of these processes will be a challenge for motivated young students at the same time as providing them with an excellent opportunity to learn different approaches. The graduate program is integrated into the Humboldt University’s International Masters - MD/PhD Program Medical Neurosciences.

Speaker: Prof. Dr. Helmut Kettenmann, Prof. Dr. Frauke Zipp

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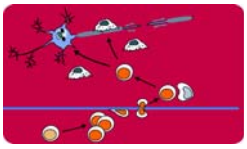

GRK 1123 "Zelluläre Mechanismen von Lernen und Gedächtniskonsolidierung in der hippokampalen Formation"

Das Graduiertenkolleg bietet die Möglichkeit, zelluläre Mechanismen von Lernen und Speicherung von Informationen im Gedächtnis sowie der Gedächtniskonsolidierung zu untersuchen. Ein Verständnis dieser Vorgänge ist von herausragender bio-medizinischer Bedeutung, da sie zum einen die Fähigkeit eines Organismus bestimmen, sich unabhängig von genetisch determinierten Verhaltensweisen an neue Umweltbedingungen anzupassen: das explizite Gedächtnis bestimmt entscheidend das menschliche Verhalten und ist Vorrausetzung für die eigene Individualität. Zum anderen sind die zugrunde liegenden Mechanismen störanfällig und damit in verschiedene neurologische und psychiatrische Krankheiten involviert. Hierzu zählen z. B. die Temporallappenepilepsie und die Alzheimersche Erkrankung. Zu den am intensivsten untersuchten zellulären Modellen für Lernen und Gedächtnis zählen die Langzeitpotenzierung (LTP) und Langzeitdepression (LTD). Allerdings sind noch viele der beteiligten prä- und postsynaptischen Mechanismen weitgehend unverstanden. Um langanhaltend Information zu speichern und Gedächtnisinhalte zu konsolidieren, bedarf es der Geninduktion und der Translation spezifischer Proteine, die die zugrunde liegenden Veränderungen in neuronalen Netzwerken ermöglichen. Auf zellulärer und neuronaler Netzwerkebene könnten an der Gedächtniskonsolidierung die Ausbildung von sharp wave ripple Komplexen, die Formierung von Frequenzgedächtnis und eine niederfrequent induzierte heterosynaptische LTP beteiligt sein. Zusätzlich könnten gespeicherte Informationen während des Traumschlafes wieder aktiviert werden, wobei die neuronale Aktivität von Theta- und Gammaoszillationen überlagert ist. Hierdurch können Veränderungen synaptischer Kopplung weiter verstärkt werden und schließlich aus dem Hippokampus in andere Hirnareale übertragen werden. Jeder der 11 am Graduiertenkolleg beteiligten Tutoren wird zu diesen Problemen spezifische Expertise beitragen. Elektrophysiologische, zellbiologische, genetische und verhaltensphysiologische Methoden sowie Modellierung von Netzwerkeigenschaften bieten den Studenten des Graduiertenkollegs die Möglichkeit, zu diesem aufregenden Gebiet der Neurowissenschaften beizutragen mit hervorragenden Chancen, eine exzellente Ausbildung in modernen neurobiologischen Methoden zu erhalten.

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Graduate Training Program learning & memory

Berlin School of Mind and Brain

The focus of the school is on the interface of humanities and behavioral sciences (philosophy, social sciences, linguistics, behavioral and cognitive psychology) with neurosciences (neurophysiology, psychiatry, computational neuroscience, neurobiology). Research concentrates on the following topics: "conscious and unconscious perception", "decision-making", "language", "brain plasticity and lifespan ontogeny" and "mental disorders and brain dysfunction".

During the first year of their dissertation Mind and Brain doctoral students take part in ten weeks of research-related instruction:: Neurophysiology, Systems and Cognitive Neuroscience, Neuroscience Methods, Behavioral Research Methods and Experimental Design, Basic Philosophical Concepts and Introduction to the Philosophy of Mind, Computational Neuroscience, Cognitive Science, Clinical Neuroscience, Advanced Issues in Philosophy of Mind and Practical Philosophy, Language and the Brain (20 CP).

Generally, students work closely with their supervisors on designing a curriculum that caters to their specific needs and interests and fosters their development in becoming well-grounded mind and brain researchers.

During the second and the third year of the doctoral program the focus is on the writing and completion of the dissertation.

Throughout the three-year program students attend an international lecture series, journal and methods clubs, poster presentations, conferences and workshops (5 CP). They are obliged to take a number of scientific soft skills courses, such as presentation skills, grant-application writing, scientific writing (5 CP), and are offered dissertation coaching, mentoring, and career advice.

The school's faculty comprises researchers of Humboldt-Universität, Freie Universität, Technische Universität, Max Planck Institute for Human Development (all based in Berlin), Universität Potsdam, Universität Magdeburg, Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig.

Speaker: Prof. Dr. Michael Pauen

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Berlin NeuroImaging Center (BNIC)

Das Berlin NeuroImaging Center ist ein Berlin-weites Verbundprojekt, das die FU und die PTB einschließt und an der Charité koordiniert wird. Die übergeordneten Themen des Berlin Neuroimaging Center ergeben sich aus den langjährigen wissenschaftlichen Schwerpunkten der beteiligten neurowissenschaftlichen Institutionen in Berlin. Es sind dies die Erforschung zerebrovaskulärer Erkrankungen, insbesondere des Schlaganfalls und damit eng verknüpft das Forschungsgebiet der neurovaskulären Kopplung. Zerebrovaskuläre Erkrankungen stellen eine große medizinische Herausforderung dar. Zwar bedeuten neuere Verbesserungen im Bereich bildgebender Verfahren einen wichtigen Durchbruch für ihr besseres Management, allerdings besteht weiterhin ein unzureichendes Verständnis der physiologischen und pathophysiologischen Mechanismen beim (individuellen) Patienten mit Schlaganfall. Darüber hinaus können die zur Zeit eingesetzten bildgebenden Techniken nicht direkt am Patientenbett angewendet werden, so dass ihre Bedeutung hinsichtlich akuter Therapiemöglichkeiten in der Klinik eingeschränkt ist. Um diese methodischen Limitierungen zu überwinden, beabsichtigen wir mit dem hier vorgeschlagenen Zentrum Erkenntnisse zusammenzuführen, die in einem multimodalen Ansatz mit unterschiedlichen bildgebenden Verfahren gewonnen wurden. Damit sollen grundlegende physiologische und pathophysiologische Zusammenhänge aufgeklärt und neue Technologien zur Anwendung am Patientenbett entwickelt werden.

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Klinische Forschergruppe "Molecular Mechanisms of Opioid Analgesia in Inflammatory Pain"

Our group is interested in mechanisms of inflammatory pain and its inhibition by opioids outside the CNS. Opioids remain the major therapy for severe acute (e.g. postoperative) and chronic (e.g. cancer-related) pain. However, serious side effects such as sedation, respiratory depression, dependence and addiction resulting from the opioid action in the CNS limit their therapeutic applications. Studies of our and other groups have provided evidence on effective analgesia, free of CNS adverse effects, after activation of opioid receptors on peripheral sensory nerves. This can be achieved by opioid application directly into peripheral injured tissues or by administration of opioids with limited CNS access. Moreover, endogenous opioid peptides, such as endorphin, are produced by immune cells accumulating in inflamed tissues. Activation of such opioid-cells by stressful stimuli, application of cortictoropin-releasing factor, adrenergic drugs or chemokines liberates opioids. Currently the following topics are being investigated:

- Transcriptional regulation of the endorphin precursor proopiomelanocortin in lymphocytes: influence of cytokines and the JAK/STAT pathway.
- Subcellular pathways of opioid peptide synthesis, processing and release from leukocytes.
- Analgesic and antiinflammatory actions of leukocyte-derived opioids by stimulating their secretion and by inhibiting their enzymatic degradation in animal models and patients with arthritis.
- Opioid peptides and receptors in leukocytes and the control of neuropathic pain.
- Opioid receptor coupling with potassium channels in peripheral sensory neurons.
- Perineurial barrier function and effective opioid analgesia.
- Kinin receptors in the generation of pain and its inhibition by interactions with peripheral opioid receptors.
- TRPV1 and TRPA1 channels and peripheral opioid analgesia.
- Role of nanocarriers and tight junction proteins in the delivery of analgesic drugs.
- Delineation of central versus peripheral components in the inhibition of clinical pain.

We use histological, biochemical, molecular, electrophysiological and in vivo pain testing methodologies combined with clinical studies in patients.

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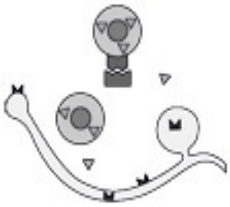

International Graduate Program Medical Neurosciences

The MSc program is divided into 5 modules and a research phase including the Master thesis. The 1st module is an intensive teaching block covering the neurobiology of the brain in health and disease from the molecular to the systems level. Module 2 encourages students to develop their individual research focus. In module 3, students are introduced to a number of relevant methods and techniques. A number of complementary skills like statistical data analysis and communication make up module 4. Students gain their first practical lab experience in module 5, the lab rotations. It is in the research phase that students combine the expertise gained in modules 1 to 5 and investigate a set of questions in great detail, perform experiments, analyze results and write a thesis.

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

Speaker: Prof. Dr. Ulrich Dirnagl

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Berlin, Charité
International Graduate Program
Medical Neurosciences

Bernstein Center for Computational Neuroscience Berlin

The Bernstein Center for Computational Neuroscience Berlin (BCCN Berlin) is a cooperation project of Humboldt-Universität zu Berlin, Technische Universität Berlin, Freie Universität Berlin, Charité Universitätsmedizin Berlin, Fraunhofer First, Max-Delbrück-Zentrum and Wissenschaftskolleg zu Berlin. It is funded by the Federal Ministry of Education and research and part of the National Bernstein Network Computational Neuroscience, Germany.
"Precision and Variability" is the research focus of the BCCN Berlin. It addresses to the question: ""How is it possible that we can react to sensory stimuli with millisecond precision if intermediate processing elements – on the level of single synapses, single neurons, small networks and even large neural systems - vary significantly in their response to the same repeated stimulus?" In particular, the Center studies whether neural variability is an inevitable consequence of the underlying biophysics and thus simply "noise", or whether such an interpretation reflects our still limited knowledge about the fundamental principles of brain-like computation.
The Center has established an international Master and PhD Program in Computational Neuroscience. The Master Program runs for 2 years and is taught by the faculty of the BCCN Berlin. It is by now in its second year. The PhD Program and the assigned fellowships started in 2007.

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Integrated Center for Research and Treatment „Center for Stroke Research Berlin"(CSB), (BMBF-Fördernummer 01 EO 0801)

The Center for Stroke Research Berlin (CSB) is dedicated to broadening therapy options and treading new roads in university medicine with exemplary methods, testing innovative mechanisms on clinically relevant models. In patient care, the CSB will foster an understanding of stroke as a chronic disease with heterogeneous causes which can be effectively met only with an interdisciplinary approach. Conditions for clinical studies at the CSB, from pre-hospital management to early rehabilitation, have been optimized and clinical research professionalized with young talent being trained specifically as "clinical scientists".

CSB research areas:
Vascular System: Mechanisms which lead to stroke and thus on the physiology and pathophysiology of the brain's blood supply.
Damage and Repair Mechanisms: Mechanisms of tissue damage and cell death, as well as endogenous repair mechanisms. In addition, basic research on mechanisms of regeneration and plasticity are integrated with projects on early and later rehabilitation.
Rehabilitation: Rehabilitation and restoration of functional loss.
Telemedicine: The use of telemedicine in the acute phase of stroke is going through the transition from the testing period to routine usage. Telemedicine also opens new vistas in the areas of the chronic phase and in computer-supported rehabilitation in the patient's own home.
Brain and Immune System: Investigation of the interaction between various body systems. Prototypical examples are the interactions between the brain and the immune system or the brain and the cardiovascular system.
Heart and Brain: Heart disease and stroke share much in common in terms of risk factors, treatment and prognosis.
Stroke and Depression: Post-stroke depression is the most common psychiatric complication after stroke and could affect up to 50% of patients. The mechanisms have hardly been researched.
Imaging: Alongside the methods in common use, molecular imaging and non-invasive near-infrared fluorescence imaging are being explored.

Speaker: Prof. Dr. Matthias Endres
Prof. Dr. Ulrich Dirnagl

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CSB
Center for Stroke Research Berlin

Competence Network Dementia (CND): Therapy Module

The Competence Network Dementia (www.kompetenznetz-demenzen.de), founded in 2002, is an association of leading german university memory clinics in the field of dementia research.
About one million people in Germany are suffering from dementia today. We can expect that this number increases dramatically within the next decades due to the increasing life expectancy. The CND sets out to improve the medical care of dementia patients by concentrating research activities and accelerating the transfer of current research findings into practical applications. Today, for example the CND has developed and validated novel biomarkers for Alzheimer dementia in CSF and blood. Most importantly, a centralized enduring bank of biomaterials (cerebrospinal fluid, serum, DNA etc.), MRT images and clinical data for recruited cases with dementia was established. The combined data- and biomaterial bank represents one of the worldwide most comprehensive longitudinal follow up studies in dementia research.
The therapy module of the CND represents a nationwide clinical infrastructure which carries out double-blind pharmacological studies in Mild cognitive impairment (MCI) and early Alzheimers disease (AD).
The therapy module of the CND is currently running two clinical trials:
1. The AD-Combi study: The primary objective of the AD-Combi trial is to test whether the combination of Galantamine plus Memantine improves memory/cognitive performance to a larger extent than Galantamine alone in AD subjects. Co-primary objective is to test whether the combination is more effective than monotherapy in delaying clinical progression of dementia. The AD-Combi study was started in 05/2005, recruitment ended in 01/2008. All patients are now in the follow-up observation period. The AD-Combi study will be completed within the first quarter of 2009.
2. The SIMaMCI study: Primary hypothesis of the SIMaMCI trial is to test whether Simvastatin significantly reduces the conversion rate to Alzheimer's disease in patients with MCI as compared to MCI patients receiving placebo. Secondary hypotheses are (1) The benefit from simvastatin treatment is larger in patients with a low level of ß-amyloid / increased level of Tau in CSF as compared to patients above/below the respective cut-off values. (2)The benefit from simvastatin treatment is larger in APO-E4 allele carriers than in other APO-E allele individuals. Recruitment is expected to start in the second half of 2008.
Both clinical trials are funded by the German Federal Ministry of Education and Research (BMBF).

Speaker:
Prof. Dr. Isabella Heuser

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Kompetenznetz Demenzen

Final Colloquium of the SFB 507

Cortex – Cooperation in Research and Training for European Excellence in the Neurosciences

Under the acronym of cortex graduate schools in Berlin, Bochum, Helsinki, London, Oslo, Prague, Stockholm, Zurich offer a joint PhD training scheme funded by the EU under the Marie Curie Mobility Action Early Stage Training (EST).

Brain cells die following trauma, stroke and in chronic neurodegenerative disease. The mature brain cannot replace lost nerve cells in, and of, itself. An important goal of treatment and prevention is therefore to minimize nerve cell death. However, recently and quite unexpectedly, experimental strategies have emerged to foster regeneration in the CNS. In addition to understanding the complex mechanisms of brain damage, we must understand how the nervous system develops and continues to change throughout life. This information has profound implications for the treatment of nervous system diseases. Harnessing the capacity of the nervous system to adapt by reactivating developmental mechanisms allows for great hopes in regards to restoring function in the injured or diseased brain. Cortex scientists and students will study the basic mechanisms of damage of common brain disorders as well as the development of the CNS to harness the ability of the CNS to adapt when challenged.

The cortex neuroscience schools each cover a broad range of neuroscience expertise in the fields of brain damage, regeneration, and development of the CNS. Bridging from the molecular to the behavioral and clinical level is a common theme of the Cortex partners. However, each cortex member school has one or several unique areas of excellence. Bringing together these complementary fields of excellence within cortex offers young doctoral students the entire panoply of neuroscientific possibilities and technologies which are available in modern neuroscience, leading to an optimally structured PhD of the highest quality.

The Berlin program has a major focus on translational aspects of neuroscience: ‚bedside to bench', as well as ‚bench to bedside'. Acute neurodegeneration (stroke), neuroinflammation (MS) and neuroimaging, are key topics on the research agenda.

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cortex
Cooperation in Research and Training for European Excellence in the Neurosciences

Cluster of Excellence "NeuroCure: towards a better outcome of neurological disorders." EXC 257

Neurological disorders contribute to more than 35% of overall disease burden in Germany, and with an aging society, this number will be increasing further. Therefore, the costs – both for the patients and their loved ones as well as for treatment and long-term health care – grow, too. In addition, the current treatments available offer relief at best but no cure. Recently, however, major advances, to which Berlin's neuroscientists contributed signifi cantly, have been made in understanding the pathophysiologicial processes underlying such disorders, thereby promising new avenues of intervention that could eventually lead to cure.

Responding to such needs, we propose to form NeuroCure, which will serve as an interdisciplinary consortium and will unite neuroscientists, basic researchers, and clinicians alike on one campus, independent of their current institutions. NeuroCure will be committed to a strong translational research approach. Due to the wealth of knowledge and acclaimed international success of Berlinbased neuroscientists working in the areas of cerebrovascular diseases, neuroinfl ammation, and disorders of network formation, the initial focus will be on stroke, multiple sclerosis, as well as on focal epilepsies and cns disturbations due to mitochondrial dysfunction. These neurological disorders are known to have overlapping pathophysiological cascades.

The ultimate goal of NeuroCure is to bring the benefi ts of our research to society. NeuroCure therefore intends to draw on the combined expertise in clinical trials from university as well as from non-university institutions and industrial partners to ensure that our 'bench-to-bedside' approach has every chance of success.

Building on innovative programs for promoting early-stage scientists (e.g. the Graduate Program 'Medical Neurosciences') and established structures (e.g. the Neurowissenschaftliches Forschungszentrum) as well as core facilities (e.g. the Berlin NeuroImaging Center) for interdisciplinary research, funding of NeuroCure will enable us:

* to recruit complementing tenure-track faculty for key research areas
* to establish intramural flexible funds to start-up interactive and innovative projects allocated according to outstanding scientific merit and monitored by peer-review
* to set-up an animal research unit for long-term outcome and behavioral analysis
* to found the NeuroCure Clinical Research Center (NCRC) inspired by highly successful counterparts in the US, and to be the first of its kind in Europe

Speaker:
Prof. Dietmar Schmitz

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www.neurocure.de

NeuroCure
Towards a better outcome of neurological disorders

Final Colloquium of the SFB 507

Research Unit: Conflicts as Signals in Cognitive Systems

The general goal of the research group on "Conflicts as Signals in Cognitive Systems" proceeds from a different assumption, namely that conflicts can be viewed as signals that are utilized to optimize information processing in the cognitive system.
Consequently, our research focuses on increasing our understanding of the interaction between conflict signals and subsequent processes of optimization within the system, on unraveling the neuronal implementation of the mechanisms mediating between the registration of a conflict and subsequent processing modulations, on identifying ontogenetic modifications of the nature of the interaction between conflicts and processes of optimization over the life course, and on determining the roles of individual differences and affects in conflict identification and utilization.
Conflicts in cognitive systems arise when at least two incompatible behavioral tendencies or motivations co-exist (Dornette/Pulkowski, 1974).
By far most of the existing research on conflicts in cognitive system has been based on the assumption that conflicts reflect incompatible tendencies between inflexible elementary properties of the system that were developed in the course of the evolution because of environmental pressures.
According to this view, the study of conflicts increases our understanding of the elementary properties of cognitive systems. These properties are often assumed to relate to the architecture of the system, on the one hand (e.g., limited capacity, simultaneous multi-level information processing), and to processing within the system, on the other hand (e.g., selection of input information and behavior, differentiation between relevant and non-relevant memory representations).
Subprojects:
Stephan Brandt (Charité), Herbert Hagendorf (Dept. of Psychology, Humboldt-University): Adaptive Attentional Processing following Conflict
Peter Frensch (Dept. of Psychology, Humboldt-University): Conflicts as Triggers for Optimizing Strategies
Arthur Jacobs (Dept. of Psychology, Freie Universität): Cognitive-Affective Control in Implicit and Explicit Reproduction
Ulman Lindenberger und Shu-Chen Li (Max Planck Institute for Live-Span Development): Conflict Monitoring across the Lifespan: Functions and Mechanisms
Werner Sommer (Dept. of Psychology, Humboldt-University): Emotions in Cognitive Conflicts
Birgit Stürmer (Dept. of Psychology, Humboldt-University), Stephan Brandt (Charité): On the Specificity and Intentionality of Adaptations triggered by Conflicts
Oliver Wilhelm (Institute for Progress in Education (IQB) Humboldt Universität zu Berlin) Interindividual Differences in overcoming Conflicts in Choice Response Tasks

Speaker: Prof. Dr. Werner Sommer; Prof. Dr. Peter Frensch, Dr. Birgit Stürmer
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Conflicts as Signals in Cognitive Systems

Keywords

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