June 10 - 11, 2010

Program Abstracts

BNF2010

Berlin Neuroscience Forum 2010

Liebenwalde

The Berlin Neuroscience Forum 2010 is sponsored by

World Precision Instruments Germany GmbH
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This meeting is a joint activity of

SFB „"Theoretische Biologie"

SFB „Entwicklungsstörungen im Nervensystem"

SFB Transregio „Gehirn als Ziel von entzündlichen Prozessen"

GRK „Zelluläre Mechanismen von Lernen und Gedächtniskonsolidierung hippocampaler Formation"

GRK „Neuropsychiatrie und Psychologie des Alters"

GRK „The Impact of Inflammation on Nervous System Function"

Berlin Neuroimaging Center

IFB-Zentrum für Schlaganfallforschung (CSB)

DFG-Forschergruppe „Konflikte als Signale"

NeuroCure Exzellenzcluster

Klinische Forschergruppe „Molekulare Mechanismen der Opioidanalgesie bei Entzündungsschmerz"

Interdisziplinäres Wolfgang Köhler-Zentrum zur Erforschung von Konflikten in intelligenten Systemen

Studiengang „Medizinische Neurowissenschaften"

Promotionskolleg „Computational Neuroscience"

Bernstein Center for Computational Neuroscience

Berlin School of Mind and Brain

Program Committee

Ingolf Blasig
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Poster Jury

Anja Bräuer
Rudolf Deisz
Martin Falcke
Carmen Infante-Duarte

Organization

Prof. Dr. Helmut Kettenmann
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Max-Delbrück-Centrum für Molekulare Medizin (MDC) Berlin-Buch
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Homepage

http://bnf2010.glia.mdc-berlin.de

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General Information

Registration	Thursday, June 10, 2010	**11.00 - 13.00**
Office Hours	Thursday, June 10, 2010 Friday, June 11, 2010	**11.00 - 19.30** **8.30 - 17.45**
Office Phone	0160 90218506	
Poster Boards	Height : 120 cm Width: 100 cm	
Poster Sessions	**Poster Session I** Poster No. 1- 35 Thursday, June 10, 2010 !!! Posters must be removed immediately after the poster session on Thursday !!!	**16.05 - 18.00**
	Poster Session II Poster No. 36 - 72 Friday, June 11, 2010	**14.30 - 16.30**
Duration of Oral Presentations	**Invited Speakers**	45 min (talk) 15 min (disc.)
	Welcome to Berlin Presentations	20 min (talk) 10 min (disc.)
	Oral Presentations	15 min (talk) 5 min (disc.)

Scientific Program

Thursday, June 10, 2010

11.00 – 13.00 Arrival and Registration

12.00 – 13.00 Lunch

13.00 – 13.05 Welcome: Helmut Kettenmann

13.05 – 14.05 Lecture I
Chair: Constance Scharff
Mathew Diamond
SISSA, Settore Neuroscienze Cognitive, Triest, Italy
NEURONAL REPRESENTATION OF TOUCH-GUIDED BEHAVIOR IN RATS

14.05 – 16.05 Welcome to Berlin Session I
Chair: Gabriel Curio
Felix Blankenburg
Department of Neurology and Bernstein Center for Computational Neuroscience, Berlin
PROBING CAUSALITY IN NEUROIMAGING BY COMBING TMS WITH FMRI

Björn Schroeder
Max Delbrück Center for Molecular Medicine(MDC) Berlin-Buch
THE TMEM16 FAMILY OF ION CHANNELS: CHLORIDE, CALCIUM, AND MORE

Christian Rosenmund
NWFZ, Charité - Universitätsmedizin Berlin
VESICULAR GLUTAMATE TRANSPORTERS: ROLES BEYOND GLUTAMATE UPTAKE INTO SYNAPTIC VESICLES

Diego Walther
Neurochemistry Group and Mouse Lab, Max-Planck-Institute for Molecular Genetics, Berlin
PSYCHIATRIC IMPLICATIONS OF RNA EDITING IN THE SEROTONERGIC SYSTEM

Thursday, June 10, 2010

16.05 – 18.00 **Poster Session I and Coffee Break**

18.00 – 19.00 **Oral Presentations Session I**
Chair: Anja Bräuer

Philipp Mergenthaler
Department of Experimental Neurology, Center for Stroke Research, Charité - Universitätsmedizin Berlin, Berlin
MITOCHONDRIAL HEXOKINASE II PROTECTS AGAINST HYPOXIC CELL DEATH BY INTERACTING WITH PEA-15

Martin Falcke
Math. Cell Physiology, Max Delbrück Center for Molecular Medicine, Berlin-Buch
RANDOM BUT RELIABLE: PROPERTIES OF SPIKE SEQUENCES OF IP3-INDUCED CA^{2+} RELEASE

Ana-Luisa Pina
Neurosurgery and Berlin Center for Regenerative Therapies, Charité - Universitätsmedizin Berlin
PIGMENT EPITHELIUM DERIVED FACTOR EFFECTS ON TRAUMATIC BRAIN INJURY

19.00 – 20.00 **Dinner**

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Chair: Dietmar Schmitz

Andrew Plested
Molecular Neuroscience and Biophysics, Leibniz-Institut für Molekulare Pharmakologie (FMP), Berlin
TRAPPING THE ACTIVATION MECHANISM OF GLUTA MATE RECEPTORS

Andrea Kühn
Neurology, Charité - Universitätsmedizin Berlin
PATHOPHYSIOLOGY OF MOVEMENT DISORDERS - WHAT CAN WE LEARN FROM DEEP BRAIN RECORDINGS

21.30 **Disco Night**

Friday, June 11, 2010

8.00 – 9.00 **Breakfast**

9.00 – 11.00 **Welcome to Berlin Session III**
Chair: Ingolf Blasig
James Poulet
Neuroscience, Max Delbrück Center for Molecular Medicine, Berlin
CORTICAL CIRCUITS AND BEHAVIOUR

Hauke Heekeren
Cluster Languages of Emotion, Freie Universität Berlin
MODULATORS OF HUMAN DECISION MAKING: GENES & SOCIAL INFORMATION

York Winter
Neurocure Center of Excellence at the Charité, Humboldt University of Berlin
T.B.A.

Peter Heuschmann
Schlaganfallepidemiologe, CSB Berlin
THE POTENTIAL OF PHASE 2 TRANSLATIONAL RESEARCH IN STROKE

11.00 – 11.30 **Coffee Break**

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Chair: Helmut Kettenmann
Asla Pitkänen
A.I.Virtanen Institute for Molecular Sciences, University of Eastern Finlnd, Kuopio, Finland
MOLECULAR BASIS FOR TISSUE REMODELING DURING EPILEPTOGENESIS: ROLE OF EXTRACELLULAR PROTEINASES

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13.30 – 14.30 **Oral Presentations Session II**
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Harald Prüß
Experimental Neurology, Charité - Universitätsmedizin Berlin
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Gabor Petzold
Experimentelle Neurologie, Charité - Universitätsmedizin Berlin
IN VIVO IMAGING OF BLOOD FLOW RESPONSES TO NEURONAL AND ASTROCYTIC ACTIVITY IN THE HEALTHY BRAIN AND IN ANIMAL MODELS OF NEUROLOGICAL DISEASES

Friedemann Paul
NeuroCure Clinical Resaerch Center, Charité - Universitätsmedizin Berlin
IMAGING NEURODEGENERATION IN THE VISUAL PATHWAY IN CHRONIC NEUROINFLAMMATION

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Jan Siemens
Max Delbrück Center for Molecular Medicine(MDC) Berlin-Buch
A BIVALENT TARANTULA TOXIN REVEALS A UNIQUE ROLE FOR THE OUTER PORE DOMAIN IN TRP CHANNEL GATING

Victor Tarabykin
Institute of Cell Biology and Neurobiology, Charité – Universitätsmedizin Berlin
GENETIC CONTROL OF THE CELL FATE IN THE DEVELOPING CEREBRAL CORTEX

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Bärwald, R., Muselmann, C., Meisel, A., Mergenthaler, P.
Department of Experimental Neurology, Center for Stroke Research, Charité Universitätsmedizin Berlin

2. FUNCTIONAL CHARACTERIZATION OF THE RNA-BINDING PROTEINS - FUS/TLS AND TARDBP/TDP-43
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BIMSB, Max Delbrück Center for Molecular Medicine, Berlin

3. A NOVEL METHOD FOR OPTIMAL ESTIMATION OF CORTICO-MUSCULAR COHERENCE BASED ON MULTI-CHANNEL EEG/MEG RECORDINGS
Bayraktaroglu, Z., Curio, G., Nikulin, V.
Neuorology, AG Neurophysik, Charité - University Medicine, Berlin

4. MICROCIRCUITRY IN THE MEDIAL ENTORHINAL CORTEX REVEALS A CELL-TYPE–SPECIFIC AND MODULAR ORGANIZATION
Beed, P., Bendels, M., Wiegand, H., Leibold, C., Johennig, F., Schmitz, D.
Neuroscience Research Centre, Charité - Universitätsmedizin Berlin

5. THE POSTSYNAPTIC 5-HT1A-RECEPTOR AND THE EFFICACY OF ANTIDEPRESSANTS IN THE PORSOLT SWIM-TEST
Bert, B., Günther, L., Rothe, J., Fink, H.
Institute of Pharmacology and Toxicology, School of Veterinary Medicine, Freie Universität Berlin

6. IMPROVING OPTICAL COHERENCE TOMOGRAPHY SENSITIVITY AND SPECIFICITY IN MULTIPLE SCLEROSIS BY ANALYSIS OF RETINAL NERVE FIBER LAYER SHAPE
Bock, M., Bischoff, S., Mansow-Model, S., Brandt, A.U., Paul, F.
NeuroCure Clinical Resaerch Center, Charité - Universitätsmedizin Berlin

7. NEUROD FAMILY TRANSCRIPTION FACTORS NEX AND NDRF REGULATE NEOCORTICAL REMOTE AXOGENESIS
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Institut für Zell- und Neurobiologie, Charité - Universitätsmedizin Berlin, Zentrum für Anatomie, Berlin

8. HIGH CONTENT MICROSCOPY ON NOCICEPTIVE NEURONS
Buschow, R., Isensee, J., Hucho, T.
Human Molecular Genetics, Max Planck Institute for Molecular Genetics, Berlin

9. EFFECTS OF CORTICOSTERONE ON HIPPOCAMPAL GAMMA OSCILLATIONS
Caliskan, G. , Heinemann, U.
Institute for Neurophysiology, Charité - Universitätsmedizin Berlin

10. INVESTIGATION OF THE FRACTALKINE RECEPTOR CX3CR1 AS A DIAGNOSTIC MARKER OF MULTIPLE SCLEROSIS
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Cecilie Vogt Klinik für Immunologie, Charité - Universitätsmedizin Berlin

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Coiro, P., Bräuer, A.U.
Institute für Anatomie, Charité - Universitätsmedizin Berlin

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Cuevas, E., Toraiwa, J., Rybak, A., Wulczyn, F.G.
Institut für Anatomie Zell- und Neurobiologie, Charité - Universitätsmedizin Berlin

13. NEURONAL CHLORIDE TRANSPORT IN HUMAN AND RAT NEOCORTEX
Deisz, R.A., Lehmann, T.-N., Horn, P., Dehnicke, C., Nitsch, R.
Institute for Cell Biology and Neurobiology, Charité - Universitätsmedizin Berlin

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Neuropathology, Charité - Universitätsmedizin Berlin

15. EFFECTS OF HISTAMINE ANTAGONISTS AND POTASSIUM CHANNELS BLOCKERS ON GAMMA OSCILLATIONS
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Institute für Neurophysiology, Charité - Universitätsmedizin Berlin

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Neuropsychiatry and Laboratory of Molecular Psychiatry, Charité - Universitätsmedizin Berlin

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Franzoni, E., Fuchs, H., Rybak, A., Wulczyn, G.F.
Institute of Cell Biology and Neurobiology, Charité - Universitätsmedizin Berlin

18. DISTINCT MUSCARINIC ACETYLCHOLINE RECEPTOR SUBTYPES MEDIATE PRE- AND POSTSYNAPTIC EFFECTS IN RAT NEOCORTEX
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Institute for Cell Biology and Neurobiology, Charité - Universitätsmedizin Berlin

19. A NEW APPROACH TO SPINAL CORD INJURY LESIONS
Glumm, J., Markovic, D., Kiwit, J.C.
Department of Neurosurgery, HELIOS Klinikum Berlin Buch, Berlin

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Gröschel, M., Müller, S., Götze, R., Ernst, A., Basta, D.
Department of Biology, Humboldt-University of Berlin

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Gurgenidze, S., Maziashvili, N., Gloveli, T., Dugladze, T.
Institute of Neurophysiology, Charité - Universitätsmedizin Berlin

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Cecilie-Vogt-Klinik für Molekulare Neurologie, Charité - Universitätsmedizin Berlin

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Institute of Medical Microbiology, Otto von Guericke University Magdeburg

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Neuropathology, Berlin

25. PARACELLULAR TRANSPORT OF AS006 - A NOVEL PAIN RELIEVING DRUG - IS AUGMENTED BY THE ABSORPTION ENHANCER CHITOSAN
Heydt, M., Amasheh, S., Grobosch, T., Lang, L. J., Stein, C.
Klinik für Anaesthesiologie und operative Intensivmedizin, Charité - Universitätsmedizin Berlin

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Biology, Humboldt University of Berlin

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Institute for Theoretical Biology, Berlin

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Charité - Universitätsmedizin Berlin

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Klinische Neurobiologie, Charité - Universitätsmedizin Berlin

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Klaft, Z.-J., Schulz, S., Rösler, A., Heinemann, U., Gerevich, Z.
Institute for Neurophysiology, Charité - Universitätsmedizin Berlin

31. NEURODEGENERATION AND LOSS OF SYNAPTOTAGMIN 1 IN MICE DEFICIENT FOR THE ENDOCYTIC SORTING ADAPTOR STONIN 2
Kononenko, N., Maritzen, T., M. Diril, K., Jung, N., Haucke, V.
Institut für Chemie/Biochemie, FU Berlin

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Department of Neurology and Experimental Neurology, Charité - Universitätsmedizin Berlin

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Institute for Neurophysiology, Charité - Universitätsmedizin Berlin

34. EXPRESSION PATTERN OF CDK5RAP2 IN MURINE BRAIN DEVELOPMENT
Krämer, N., Issa, L., Zwirner, A., Kaindl, A.M.
Institute of Cell Biology and Neurobiology, Charité - Universitätsmedizin Berlin

35. PIGMENT EPITHELIUM DERIVED FACTOR AS AN IMMUNOLOGICAL MODULATOR
Lang, V., Ruprecht, K., Paul, F., Infante-Duarte, C., Vajkoczy, P., Piña, A.-L.
Experimentelle Neurochirurgie, Charité - Universitätsmedizin Berlin

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Institute for Cell Biology and Neurobiology, Charité – Universitätsmedizin Berlin

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Lapilover, E.G., Heinemann, U., Friedman, A.
Institut für Neurophysiologie, Charité Universitätsmedizin Berlin

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Institute of Physics, Humboldt University of Berlin

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Department of Experimental Neurology, Center for Stroke Research, Charité - Universitätsmedizin Berlin

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Neuropathology, Charité - Universitätsmedizin Berlin

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Cellular Neuroscience, Max Delbrück Center for Molecular Medicine, Berlin

42. INHIBITION OF OPIOID PEPTIDE DEGRADATION FOR ANALGESIA IN PERIPHERAL INFLAMED TISSUE
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Anaesthesiologie, Charité – Universitätsmedizin Berlin, Campus Benjamin Franklin, Berlin

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Cecilie-Vogt Klinik für Molekulare Neurologie, Charité - Universitätsmedizin Berlin

44. CELLULAR UPTAKE OF PIGMENT EPITHELIUM DERIVED FACTOR BY U87 GLIOBLASTOMA CELLS
Müller, M., Pina, A.-L.
Experimentelle Neurochirurgie, Charité - Universitätsmedizin Berlin

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Newie, I., Blasig, I.E.
Leibniz-Institut für Molekulare Pharmakologie (FMP), Berlin

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Center for Stroke Research Berlin, Charité - Universitätsmedizin Berlin

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Graduate Program Medical Neuroscience, Berlin

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Cortical Development, Max Planck Institute for Experimental Medicine, Goettingen

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NeuroCure Clinical Research Center, Charité - University Medicine, Berlin

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Institute of Cell Biology and Neurobiology, Charité - Universitätsmedizin Berlin

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FMP/NeuroCure, AG Physiology of Network Representations, Berlin

52. SILENCING NEURONAL ACTIVITY WITH A DESIGNER RECEPTOR ACTIVATED BY A DESIGNER DRUG
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AG Schmitz, Neuroscience Research Center, Charité - Universitätsmedizin Berlin

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Klinik für Psychiatrie und Psychotherapie, Charité - Universitätsmedizin Berlin

54. A YEAST TWO HYBRID SCREEN FOR INTERACTION PARTNERS OF TRPV1, TRPM8 AND TRPA1
Schlacks, D., Siemens, J.
Neuroscience, Max Delbrück Center for Molecular Medicine, Berlin

55. MAGNETIC RESONANCE ELASTOGRAPHY DETECTS REDUCED VISCOELASTICITY IN AN ANIMAL MODEL OF CNS DEMYELINATION
Schregel, K., Wuerfel, E., Petersen, D., Sinkus, R., Wuerfel, J.
Institute of Neuroradiology, University Luebeck

56. PKC EPSILON IN PROTEIN TRANSLATION
Schreier, J., Isensee, J., Hucho, T.
Prof. Dr. H.-H. Ropers, Max-Planck Institute for Molecular Genetics, Berlin

57. TRANSIENTLY DECREASED EXTRACELLULAR ATP CONCENTRATION DURING THE ONSET OF HIPPOCAMPAL GAMMA NETWORK OSCILLATIONS
Schulz, S.B., Klaft, Z.J., Heinemann, U., Gerevich Z.
Institute of Neurophysiology, Charité - Universitätsmedizin Berlin

58. DEVELOPMENTAL AND CELL TYPE-SPECIFIC EXPRESSION OF THYROID HORMONE TRANSPORTERS IN THE MOUSE BRAIN AND PRIMARY BRAIN CELLS
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Institut für Experimentelle Endokrinologie, Charité - Universitätsmedizin Berlin

59. MICROGLIAL CALCIUM SIGNALING IN SITU
Seifert, S., Färber, K., Kettenmann, H.
Cellular Neuroscience, Max Delbrück Center for Molecular Medicine, Berlin

60. THE ROLE OF SATB2/CTIP2 AND FEZL IN CORTICAL CONNECTIVITY AND THE ELUCIDATION OF THEIR DOWNSTREAM PATHWAYS
Paraskevi Sgourdou, Camino de Juan Romero, Olga Britanova and Victor Tarabykin
Cortical Development Group, Max Planck Institute for Experimental Medicine, Goettingen

61. LYSOPHOSPHOLIPID ACID(LPA) CONTROLS AXONAL OUTGROWTH VIA PRG-1/RAS GRF-2 INTERACTION
Soriguera, A., Bardehle, S., Hoffmann, S.A., Swiercz, J.M., Offermanns, S., Nitsch, R., Bräuer, A.U.
Molecular Neurobiology Research Group, Institute for Cell Biology and Neurobiology Charité-Universitätsmedizin Berlin

62. STRONG INFILTRATION OF REGULATORY T CELLS INTO THE CNS 14 DAYS AFTER ENTORHINAL CORTEX LESION AND MIDDLE CEREBRAL ARTERY OCCLUSION
Stubbe T., Richter D., Meisel C., Nitsch R., Brandt C.
Institute of Cell Biology and Neurobiology, Charité - Universitätsmedizin Berlin

63. THE EFFECT OF SODIUM-CAPRATE ON PLASMA MEMBRANE LOCALIZATION OF CLAUDIN-5
Tscheik, C., Blasig, I.E.
Leibnitz-Institut für Molekulare Pharmakologie (FMP), Berlin

64. MINOCYCLINE ATTENUATES THE MICROGLIA-ASSISTED GLIOMA EXPANSION AND INVASION
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Cellular Neurosciences, Max Delbrück Center for Molecular Medicine, Berlin

65. REDUCED HYPERPOLARIZATION-ACTIVATED CATION CURRENTS IN TEMPORAL LOBE EPILEPSY
Wierschke, S., Horn, P., Dehnicke, C., Bräuer, A.U., Deisz, R.A.
Institute for Cell Biology and Neurobiology, Charité - Universitätsmedizin Berlin

66. BETA-ADRENERGIC RECEPTOR ACTIVATION INDUCES LONG-LASTING POTENTIATION IN BURSTING BUT NOT REGULAR FIRING CELLS AT CA1-SUBICULUM SYNAPSES
Wojtowicz, A., Fidzinski, P., Heinemann, U., Behr, J.
Department of Neurobiology, Charité - Universitätsmedizin Berlin

67. BURST-LIKE SPIKE PATTERNS IN A RESONATE-AND-FIRE MODEL NEURON
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Institute for Theoretical Biology, Humboldt University of Berlin

68. GAMMA OSCILLATIONS WITHIN THE SUBICULUM IN VITRO
Zarnadze, S., Schmitz, D., Gloveli, T.
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69. CLAUDIN-DERIVED PEPTIDES FOR MODULATION OF THE BLOOD-BRAIN BARRIER (BBB) PERMEABILITY
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Leibnitz Institut für Molekulare Pharmakologie, Berlin

70. TEASHIRT1 IS ESSENTIAL FOR THE DEVELOPMENT OF OLFACTORY BULB GRANULE CELL NEURONS
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Department of Neurosciences, Max-Delbrück-Center for Molecular Medicine, Berlin

71. MODULATIONS IN SUBTHALAMIC ALPHA ACTIVITY DURING EMOTIONAL PROCESSING CORRELATE WITH SEVERITY OF POSTOPERATIVE DEPRESSIVE SYMPTOMS IN PATIENTS WITH PARKINSON'S DISEASE
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Department of Neurology, CVK, Charité - University Medicine Berlin

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Haq, ul R., Liotta, A. , Kovacs, R. , Heinemann, U. and Behrens, C. J.
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Abstracts of Lectures

NEURONAL REPRESENTATION OF TOUCH-GUIDED BEHAVIOR IN RATS

Mathew Diamond

SISSA, Settore Neuroscienze Cognitive, Trieste, Italy

Recent research is beginning to provide a picture of how the brain, in rodents, encodes the physical features contacted objects and ultimately forms a complete representation of tactile behavior. Rats sweep their whiskers forward and backward, describing large elegant arcs. To find out how well rats can identify textures, researchers have trained them, in the dark, to take different actions according to the identity of the contacted texture (e.g. turn to the left or right reward location). Along a surface, a whisker's trajectory is characterized by an irregular, skipping motion made up of intermixed low and high velocities (sticks and slips). Discrimination occurs because each texture is associated with a distinct stick-slip trajectory. Spiking in the sensory system, from receptor to cortex, is determined by the convolution of each neuron's „filter" with the ongoing state (e.g. position, velocity, acceleration) of its principal whisker. Firing probability increases with progressively higher whisker velocity and acceleration, causing rough textures to translate to a greater rate of neuronal firing than smooth. In a direct test of the proposal that neuronal firing rate distinguishes between different texture sensations, activity was measured in cortical barrels while rats identified a contacted texture as rough or smooth. On the set of trials when the rats correctly identified the stimulus, the average firing rate of neurons was higher for rough trials than for smooth trials. But on error trials, the firing-rate code was reversed – lower for rough than for smooth – meaning that the rats made their decision (right or wrong) based upon the magnitude of whisker-evoked activity in barrel cortex. The encoding of physical features is but one aspect of the total touch-guided behavior. To better understand how sensory experiences are stored, we recorded single-unit firing and local field potentials from the CA1 region of hippocampus while rats performed a two-alternative forced-choice task where texture specified reward location. Two separate textures directed the rats to each reward location, allowing us to separate signals encoding touch from signals encoding reward location. One-third of CA1 neurons represent texture identity. Tactile information persists for several seconds after the rat breaks off contact with the texture, forming a memory trace that bridges the stimulus with the reward collection. Over half the neurons fire according to reward location and thus represent the animal's behavior. The presence of a reward location signal in a neuron does not predict the presence or absence of a tactile signal. These experiments indicate that upon stimulus contact, the CA1 population forms a texture representation and retains that signal – overlapping but independent of spatial signals – until reward collection. At this level in the brain, the contacted object is represented not as a physical feature (the whisker trajectory) but as a salient event.

MOLECULAR BASIS FOR TISSUE REMODELING DURING EPILEPTOGENESIS: ROLE OF EXTRACELLULAR PROTEINASES

Asla Pitkänen

A.I.Virtanen Institute for Molecular Sciences, University of Eastern Finlnd, Kuopio, Finland

Fifty million people worldwide have epilepsy, and in Europe the total health costs associated with epilepsy is •15.5 billion. In 65% of patients epilepsy is caused by acquired injuries like prolonged febrile seizure (or SE), stroke or traumatic brain injury (TBI). Another large group of etiologies includes developmental brain malformations. In acquired epilepsies, epilepsy typically develops in 3 phases: brain insult ð epileptogenesis ð epilepsy (spontaneous seizures). Attempts to prevent epileptogenesis after brain injury have all failed, and therefore, there is an urgent need for novel molecular targets for antiepileptogenesis. As epilepsy typically develops after brain injury that is associated with other functional impairments (e.g., motor and cognitive impairment), in optimal case the antiepileptogenic therapy would also enhance recovery. Recent molecular profiling studies have pinpointed extracellular proteinases as one prominent group of genes with altered expression during epileptogenesis. As a follow-up of these observations, we recently demonstrated an up-regulation of urokinase-type plasminogen activator (uPA) and its receptor (uPAR) during the 2-wk post-injury period after SE, which is the most active phase of tissue remodeling. Further, the deficiency of uPA or its receptor uPAR have robust efects on post-injury epileptogenesis, including delayed neurodegeneration. Data available from cancer field demonstrates the role of uPA-system in cancer cell adhesion, proliferation, differentiation and migration; matrix degradation; apoptosis and tumor angiogenesis Interestingly, apoptosis, neurogenesis, degradation of extracellular matrix, and angiogenesis are well known brain alterations occurring during acquired epileptogenesis in animals and humans. This presentation reviews the recent data available about the role of extracellular proteinases, with focus on uPA-uPAR system, on recovery and epileptogenesis after common brain insults.

Abstracts of Welcome to Berlin Presentations

PROBING CAUSALITY IN NEUROIMAGING BY COMBING TMS WITH FMRI

Felix Blankenburg

Department of Neurology and Bernstein Center for Computational Neuroscience, Charité, Berlin

In the talk, I will briefly present the research interests of the group Neurocomputation and Neuroimaging. Based on a series of fMRI and EEG experiments, a neuronal network model grounded in dynamic causal modelling (DCM) will be developed for the somatosensory system. In a first step, parameters indicating coupling between different brain areas are determined for each experiment. In a second step, a unified neurobiologically informed computational network model will then be constructed, based on the parameters obtained in the individual experiments, using Bayesian networks on the meta-experimental-level to integrate all data of the different experiments in a formal multiple -constraint manner. The architecture of this network will be extended and confirmed by simultaneous fMRI and TMS. An introduction to the recent advantage of combining TMS with fMRI will be the focus of the second part of the presentation. This new technique offers the unique opportunity to study effective connectivity in the human brain. I will discuss the technical challenges of simultaneous TMS and fMRI and their solutions and will present recent results of different studies in which this new method was successfully applied.

Supported by a grant of the BMBF

THE POTENTIAL OF PHASE II - TRANSLATIONAL RESEARCH IN STROKE

Peter U. Heuschmann

Research Group "Clinical Epidemiology and Health Services Research in Stroke – CEHRiS", Center for Stroke Research Berlin, Charité – Universitätsmedizin Berlin

The "classical" concept of translational research differentiates between phase I translational research (developing novel treatment concepts in basic sciences settings and testing them for safety and efficacy within clinical trials) and phase II translational research (translating research findings from clinical science settings into clinical practice at the community level). Phase II translational research aims to: identify specific needs in clinical practice; investigate effectiveness of treatment concepts in routine care; and assess ways of implementing research evidence into practice. Specific requirements are inherent to this type of research, e.g. mixed method approaches, availability of data from routine care, as well as close interactions between researchers, clinicians and health care providers. The Center for Stroke Research Berlin (CSB) at the Charité - Universitätsmedizin Berlin was initiated in 2008 by the Federal Ministry of Education and Research as an Integrated Center for Research and Treatment to overcome the translational roadblock in stroke medicine by integrating basic research with clinical research and clinical care. This interdisciplinary concept of the CSB is achieved by the appointment of seven new professors in different research areas together with existing research groups and by the implementation of several cross cutting modules, such as experimental laboratories or a dedicated trial team. Thus, the CSB offers a unique research environment in Germany for facilitating all types of translational research in stroke. A number as innovative projects and structures are initiated within the CSB to guarantee effective phase II translational research, comprising e.g. the areas of long-term management of stroke patients, service delivery in high risk populations and interdisciplinary treatment of rare stroke conditions. The talk will highlight the potential of phase II translational research for informing other studies within a comprehensive stroke research network, such as the CSB, and for developing new non-linear and bidirectional concepts of translational research.

PATHOPHYSIOLOGY OF MOVEMENT DISORDERS - WHAT CAN WE LEARN FROM DEEP BRAIN RECORDINGS

Andrea A. Kühn

Department of Neurology, Motor Neuroscience and Deep Brain Stimulation Group, Charité – University Medicine Berlin, Germany

A major breakthrough in therapy for Parkinson's disease (PD), dystonia and otherwise intractable movement disorders has been the introduction of deep brain stimulation (DBS) that leads to significant long-term improvement in motor symptoms. Moreover, DBS offers the unique opportunity to directly record local field potentials (LFP) from deep brain targets that are otherwise inaccessible. Latest findings from deep brain recordings have led to groundbreaking insights into human basal ganglia (BG) pathology and have challenged the classical anatomico-functional model of cortex – basal ganglia - cortex circuits. The new concepts that have emerged from this research emphasize the role of firing patterns and synchronised oscillatory activitywithin the BG-cortical network for the pathophysiology of movement disorders. Intracranial LFP recordings show disease-specific patterns of abnormal synchrony. In particular, beta band activity (~20 Hz) is generally enhanced in the BG of PD patients, but is suppressed prior to and during movement, and during levodopa treatment in parallel with clinical improvement in motor deficits. Recent findings of our group have shown that DBS also suppresses beta activity in PD. Similarly, pathologically enhanced low frequency activity (5-12 Hz) is suppressed in dystonia during DBS. Thus, there is increasing correlative evidence that abnormal synchronization may

disturb local functioning in general, and that excessive synchrony at frequencies below 35 Hz in basal ganglia-cortical loops may impair motor processing in PD and dystonia. Suppression of enhanced disease-specific activity across the cortex–basal ganglia-cortex network (by movement, levodopa or DBS) may gate local processing, and thus allow other frequencies more relevant for information coding (such as gamma band activity) to emerge.

TRAPPING THE ACTIVATION MECHANISM OF GLUTAMATE RECEPTORS

Andrew J.R. Plested

Leibniz-Institut für Molekulare Pharmakologie (FMP) & Neurocure Initiative Charité Universitätsmedezin

Glutamate receptors participate in fast excitatory transmission throughout the brain. However, the molecular composition of receptors is far from clear. Recent advances in the structural biology of glutamate receptors now allow us to begin to picture the mechanism through which binding of glutamate activates the receptor. Each receptor is composed of four subunits. These subunits are intimately entwined, with multiple points of contact that are tuned to rearrange sequentially during the activation cycle. Here I will outline our recent work that defines these interfaces in AMPA and kainate receptors, and points to the roles that individual subunits play in receptor activation. The hierarchical set of interfaces allow brief activation (essential for fast neuronal signalling) whilst retaining moderate sensitivity to glutamate. These studies might also offer opportunities for development of novel therapeutic agents.

CORTICAL CIRCUITS AND BEHAVIOUR

James Poulet

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Internal brain states form key determinants for sensory perception, sensorimotor coordination and learning . A prominent reflection of different brain states in the mammalian CNS is the distinct pattern of corticaloscillations and synchrony, as revealed by extracellular recordings of the electroencephalogram, local field potential and action potentials. Such temporal correlations of cortical activity are thought to be fundamental mechanisms of neuronal computation. We made single and dual whole-cell recordings from primary somatosensory barrel cortex in mice performing whisker behaviour to examine the cellular correlates of cortical state change. The membrane potential of nearby neurons undergo slow large amplitude fluctuations that are highly correlated during quiet wakefulness, but when the mouse is whisking, cortical neurons depolarise and undergo a state change that reduces the membrane potential fluctuations as well as the correlation between nearby neurons, resulting in a desynchronised local field potential and electroencephalogram. I will go on to discuss recent experiments examining the network mechanisms underlying the change in cortical state during whisker movements. Cortical state change persists after cutting the primary sensory nerve from the whisker pad and therefore is generated internally, within the CNS. Juxtacellular recordings from thalamic neurons during whisker movements reveal an increase in thalamic spiking activity during whisker movements. Inactivation of thalamus, by thalamic injection of muscimol, increases cortical slow fluctuations during quiet periods. During active periods cortical neurons become hyperpolarised, in contrast to the depolarised state during whisking under control conditions, and the slow fluctuations disappear. The thalamus is therefore responsible for one key aspect of the cortical state change - it provides tonic depolarising input during whisking.

Supported by H.F.S.P., NeuroCure and Deutsche Forschungsgemeinschaft.

VESICULAR GLUTAMATE TRANSPORTERS: ROLES BEYOND GLUTAMATE UPTAKE INTO SYNAPTIC VESICLES

Christian Rosenmund

Charité - Universitätsmedizin Berlin, NWFZ, Berlin

Classically, vesicular glutamate transporters (VGLUTs) transport glutamate from the cytoplasm into synaptic vesicles. Deletion of VGLUT genes disrupts synaptic glutamate release and their expression suffices to determine neurons as glutamatergic. We recently discovered that VGLUTs control additional key parameters such as quantal size and vesicular release probability, suggesting that they are fundamental regulators of synaptic strength and synaptic plasticity. In this talk I will present experiments aimed to understand these novel functions such as how number of VGLUTs per vesicle (VGLUT content) can affect the amount of stored glutamate and in addition, the probability of vesicle release. For our experiments we employ genetic, ultrastructural molecular biological and electrophysiological approaches. I will subsequently explore possible underlying mechanisms of how VGLUT copy numbers per vesicle regulate synaptic strength. Second, i will provide data on how different VGLUT paralogs contribute to functional differences in discrete synapse populations, as implied by the distribution pattern of the two main paralogs VGLUT1 and VGLUT2 in the brain.

THE TMEM16 FAMILY OF ION CHANNELS: CHLORIDE, CALCIUM, AND MORE.

Björn Christian Schroeder

Max-Delbrueck-Center for Molecular Medicine, Cellular Neuroscience, Berlin, Germany

Calcium activated chloride currents are important for the regulation of sensory transduction, epithelial secretion, neuronal excitability, smooth muscle contraction and vascular tone. Recently three groups

showed independently TMEM16A (also known as anoctamin 1) to be, at least part of, a calcium activated chloride channel (CaCC). The TMEM16 family of transmembrane proteins is conserved among eukaryotes with multiple family members upregulated in some forms of cancer. TMEM16A knock out mice show a lung phenotype similar to cystic fibrosis and die within one week after birth. TMEM16B is believed to play an important role in olfactory signal transduction, TMEM16E is linked to the three human diseases gnathodiaphyseal dysplasia (GDD), autosomal recessive limb gridle muscular dystrophy (LGMD) and Miyoshi Myophaty (MM) and TMEM16J is a p53 induced gene. Interestingly not all members of the TMEM16 family induce new currents when expressed in HEK-293 cells or salamander oocytes. A robust signal is only found for TMEM16A and TMEM16B, but moderate currents have also been reported for TMEM16F. This observation correlates with a clear plasma membrane staining found for TMEM16A-GFP, TMEM16B-GFP and TMEM16F-GFP expressing cells. Other members of the family, like TMEM16E-GFP, appear to be localized predominantly in intracellular vesicles. Either the transport of the later group is very inefficient due to a missing subunit / interaction partner, or they serve as intracellular channels.

A BIVALENT TARANTULA TOXIN REVEALS A UNIQUE ROLE FOR THE OUTER PORE DOMAIN IN TRP CHANNEL GATING

J. Siemens[1], C. J. Bohlen[2], A. Priel[2], S. Zhou[3], D. King[3], D. Julius[2]

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Toxins have evolved to target regions of membrane ion channels that underlie ligand binding, gating, or ion permeation, and have thus served as invaluable tools for probing channel structure and function. We have examined TRP channel gating mechanisms by identifying a peptide toxin from the Earth Tiger tarantula that selectively and irreversibly activates the capsaicin/heat-sensitive channel, TRPV1. This high avidity interaction derives from a unique tandem repeat structure of the toxin that endows it with an antibody-like bivalency, illustrating a new paradigm in toxin structure and evolution. The novel 'double-knot' toxin traps TRPV1 in the open state by interacting with residues in the presumptive pore-forming region of the channel. Our results argue against a presumed similarity in activation mechanisms of TRP and voltage-gated channels, implicating the outer pore domain, rather than the voltage-sensor equivalent (S4) region, as a critical determinant of TRP channel gating. *Supported by Grants from the NIH/NINDS (to D.J.) and by a fellowship from the Human Frontier Science Program Organization (HFSP, to J.S.)*

GENETIC CONTROL OF THE CELL FATE IN THE DEVELOPING CEREBRAL CORTEX

Victor Tarabykin

Cellular Neurobiology, Institute of Cell Biology and Neuro-biology, Charité – Universitätsmedizin Berlin, Campus Mitte, Schumannstr. 20/21, Berlin

During development, several populations of progenitor cells residing in the ventricular and subventricular zones in the dorsal telencephalon generate a large variety of neurons. These neurons acquire distinct morphologies, specific connections and physiological properties and serve distinct functions in the mammalian cerebral cortex. We are interested in the cellular and molecular mechanisms underlying cell fate specification in the mouse cerebral cortex. We focus on the mechanisms controlling the generation, migration and axonal guidance of neurons of different cortical layers and areas. I will discuss the roles of two transcription factors Satb2 and Sip1 in the cortical development.

PSYCHIATRIC IMPLICATIONS OF RNA EDITING IN THE SEROTONERGIC SYSTEM

Diego J.Walther

Max Planck Institute for Molecular Genetics, Neurochemistry Group & Mouse Lab, D-14195 Berlin.

Brain serotonin (5-HT) plays a key role in the regulation of mood and has been implicated in a variety of psychiatric disorders. Tryptophan hydroxylase (TPH) is the rate-limiting enzyme in the biosynthesis of 5-HT. Recently, we discovered a second TPH isoform (TPH2) in vertebrates, including man, which is predominantly expressed in brain, while the previously known TPH isoform (TPH1) is primarily a non-neuronal enzyme . Overwhelming evidence now points to *TPH2* as a candidate gene for 5-HT-related psychiatric disorders. To investigate the role of *TPH2* gene variability in the aetiology of psychiatric diseases we performed cDNA sequence analysis of *TPH2* transcripts from human *post mortem* samples obtained from individuals with psychiatric disorders, including drug abuse, schizophrenia, and suicide, and controls. We found that *TPH2* exists in two alternatively spliced variants in the coding region, which we denoted *TPH2a* and *TPH2b*. Moreover, we found evidence that the pre-mRNAs of both splice variants are dynamically RNA-edited in a mutually exclusive manner. Kinetic studies with cell lines expressing recombinant *TPH2* variants revealed a higher activity of the novel TPH2B protein compared with the previously known TPH2A, whereas RNA editing was shown to inhibit the enzymatic activity of both TPH2 splice variants. Therefore, our results strongly suggest a complex fine-tuning of central nervous system 5-HT biosynthesis by *TPH2* alternative splicing and RNA editing. Thus, not only 5-HT2C receptor editing but also TPH2 editing are involved in neuropsychiatric conditions.

Abstracts of Oral Presentations

RANDOM BUT RELIABLE: PROPERTIES OF SPIKE SEQUENCES OF IP_3-INDUCED CA^{2+} RELEASE

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Mathematical Cell Physiology, Max Delbrück Center for Molecular Medicine Berlin

In recent years we established for a variety of cell types that IP_3-induced intracellular Ca^{2+} signaling generates random spike sequences. Theoretical investigations now reveal well defined functions for the pathway components: Channel cluster properties set the average interspike interval and its standard deviation while global feedback (like ER depletion, Ca^{2+} feedback to PLC or phosphorylation) determine the maximal information content of spike trains. Ca^{2+} spike sequences exhibit also surprising robustness, since the mechanism buffers genetic and environmental variability. I will also present considerations suggesting these properties to apply to randomly spiking neurons, too.

MITOCHONDRIAL HEXOKINASE II PROTECTS AGAINST HYPOXIC CELL DEATH BY INTERACTING WITH PEA-15

Philipp Mergenthaler[1,2], Anja Kahl[1], Anne Kamitz[1], Dorette Freyer[1], Dirk Megow[1], Josef Priller[4], Ulrich Dirnagl[1], David W. Andrews[5], and Andreas Meisel[1,2,3]

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Hexokinase II is one of the hexokinase isoenzymes facilitating the first step of glucose metabolism by phosphorylating glucose. However, hexokinases have also been implicated in regulation of apoptosis. Mitochondrial binding of hexokinases, in particular of Hexokinase II, has been found to show apoptosis modifying features. While this association is located at the outer mitochondrial membrane's voltage dependent anion channel (VDAC) and stabilized by Akt-kinase, little is known about potential interacting proteins and the exact molecular mechanisms of modulating apoptosis. We found hypoxia-inducible factor 1 (HIF-1) dependent upregulation of Hexokinase II mRNA as a response to ischemic preconditioning in cultured primary rat brain cortical neurons. Furthermore, overexpression of Hexokinase II in these cultures protected neurons from apoptotic cell death in an in vitro model of cerebral ischemia (oxygen-glucose deprivation, OGD) in a glucose dependent fashion. To investigate the molecular mechanism of this antiapoptotic effect, we screened for interactors of Hexokinase II. We found Pea-15 (phosphoprotein enriched in astrocytes), an Akt-kinase regulated, ubiquitous multifunctional protein with anti-apoptotic features and involvement in glucose metabolism, as a putative interactor of Hexokinase II. Confirmatory experiments revealed interaction of Hexokinase II and Pea15 in living cells with FLIMFRET microscopy, as well as interaction in primary cortical neurons and a mitochondrial localization of this anti-apoptotic protein complex. In further experiments, we were able to prove that mitochondrial association is indispensable for the anti-apoptotic features of this interaction. In summary, our results demonstrate that interaction of Hexokinase II and Pea15 promotes cellular survival and that the interaction with Pea15 is at least in part responsible for the anti-apoptotic features of Hexokinase II. We propose that Hexokinase II serves as a molecular switch in a multiprotein complex with mitochondrial localization, regulating apoptosis in a glucose dependent fashion and thus providing a link between cellular metabolism and survival.

The research leading to these results has received funding from the European Union's Seventh Framework Programme (FP7/2007-2013) under grant agreements n° 201024 and n° 202213 (European Stroke Network).

IMAGING NEURODEGENERATION IN THE VISUAL PATHWAY IN CHRONIC NEUROINFLAMMATION

Friedemann Paul

Clinical Neuroimmunology Research Group, NeuroCure Clinical Research Center

Axonal and neuronal damage are increasingly recognized as relevant pathologic features in chronic inflammatory central nervous system disorders such as multiple sclerosis (MS). In clinical trials and for research purposes, these features are investigated with brain magnetic resonance imaging (MRI), e.g. by quantification of brain atrophy. Recently, optical coherence tomography (OCT) has emerged as a promising tool to image retinal axonal loss *in vivo* with a high spatial resolution and thus to investigate neurodegeneration in the anterior visual pathway. Small studies suggest an association between brain atrophy as quantified by MRI and decrease of the retinal nerve fiber layer thickness (RNFLT) as measured by OCT. However, a potential mutual association of RNFLT with the visual nervous system as well as with whole brain neurodegeneration still needs to be better understood. In particular, in MS the interplay between damage to the anterior and the posterior (retrogeniculate) visual pathway remains to be clarified.

We have investigated possible mutual associations between brain atrophy, RNFLT loss and alterations of the visual cortex with various MRI and OCT techniques in a large cohort of relapsing-remitting MS patients. Data from our group will be presented which provide new insight into the pathophysiology of visual dysfunction in MS and into disease-related neurodegeneration of the visual pathway.

IN VIVO IMAGING OF BLOOD FLOW RESPONSES TO NEURONAL AND ASTROCYTIC ACTIVITY IN THE HEALTHY BRAIN AND IN ANIMAL MODELS OF NEUROLOGICAL DISEASES

Gabor Petzold

Charité - Universitätsmedizin Berlin, Neurology, Berlin

Normal brain activity critically depends on a continuous supply with oxygen and glucose through cerebral blood flow (CBF). Although cerebral energetic demands are very high, the brain has only very little means of energy storage. Because of this unique characteristic, local brain activity has to be matched by a concomitant increase in local CBF (a phenomenon referred to as functional hyperemia or neurovascular coupling). Functional hyperemia is involved in the pathophysiology of many acute neurological and neurodegenerative diseases, such as stroke, hypertensive encephalopathy, Alzheimer's disease, and vascular dementia. Moreover, functional hyperemia forms the basis of many modern noninvasive functional neuroimaging techniques that use this phenomenon to map brain activity in animals and humans. Despite the importance of functional hyperemia for clinical neurology and neuroscience, the underlying mechanisms have remained largely undefined. Moreover, many different transmitters and pathways have been implicated in functional hyperemia, but the relevance of these mechanism in vivo, as well as the exact sequence of events and the different cell types involved, remain to be determined. Our goal is to study these mechanisms in the living, intact brain of anesthetized rodents, using molecular in vivo imaging techniques. We aim to define the role of different cellular pathways in functional hyperemia, and explore the perturbation of this phenomenon in animal models of stroke, Alzheimer's disease and vascular dementia.

PIGMENT EPITHELIUM DERIVED FACTOR EFFECTS ON TRAUMATIC BRAIN INJURY

Pina A.L.[1, 2,3], Casalis P.[1], Lang V.[1,2], Bruendl E.[3], Stoerr E.M.[3], Brawanski A.[3], Thomale U.[1], Vajkoczy P[1]

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Pigment epithelium-derived factor (PEDF) is a potent antiangiogenic and tumor-differentiating factor that can also protect and differentiate neurons. The neuroprotective effects of PEDF on brain cells has been demonstrated mainly by in vitro experiments showing the ability of the protein to support the survival of neurons in the presence of various neurotoxic stimuli and inducing neuronal differentiation. In this study we report the in vivo effects that PEDF exerts on neurogenesis, apoptosis and proliferation of microglia cells after traumatic brain injury (TBI). Adult male rats were sham operated or subjected to unilateral controlled cortical impact injury (CCI). Animals were divided into two groups: one for expression studies, at 4hrs, 1, 4 and 7days after CCI. In the other group, animals received PEDF and/or vehicle into the lateral ventricle as well as intraperitoneal injections of Bromo-deoxy-Uridine (BrdU) over a period of 7 days. Brain tissues from these animals were prepared for real time PCR mRNA expression or immunohistological analysis. Our results show that PEDF mRNA expression after CCI increase with time. Infusion of PEDF is associated with a reduced lesioned area with increased number of proliferating cells and diminished number of apoptotic and microglia cells. Increased number of proliferating cells into the SVZ and no changes in the DG could also be detected in comparison to controls. Our results indicate that in vivo PEDF may be a multifunctional neuroprotective agent, influencing neurogenesis, apoptosis and inflammatory processes in TBI.

NEUROFASCIN AS TARGET OF AUTOANTIBODIES IN GUILLAIN-BARRÉ SYNDROME

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Guillain-Barré syndrome (GBS) is an acute autoimmune-mediated demyelinating polyneuropathy which includes the generation of antibodies. Antibodies directed against myelin and axonal antigens involved in saltatory nerve conduction such as neurofascin appear as putative targets to boost GBS disease exacerbation. Neurofascin isoforms are expressed both at the paranodal axo-glial junction and the node of Ranvier. Neurofascin antibodies lead to complement deposition, axonal injury and impair saltatory nerve conduction. In order to investigate a role of neurofascin autoimmunity in GBS pathophysiology we quantified neurofascin antibody titers in GBS patients (n=52) compared to controls (n=44) by ELISA and Western analysis. Neurofascin autoantibody titers are significantly elevated in GBS patients. Here, we identify autoimmunity against the cell adhesion molecule neurofascin which might be relevant for the development or augmentation of the autoimmune process in GBS patients. Neurofascin antibodies might i) disrupt sodium channel function and axon

conduction at nodes of Ranvier, ii) trigger axonal injury and iii) inhibit remyelination. In addition, patients revealing high neurofascin antibody titers might be prone to develop central affection which is observed in a subgroup of GBS patients.

Poster Session I

Thursday, June 10, 2010, 16.05 - 18.00

1 CHARACTERIZATION OF A HEXOKINASE II-CENTERED MULTIPROTEIN COMPLEX MEDIATING NEUROPROTECTION

Rebecca Bärwald[1], Claudia Muselmann[1], Andreas Meisel[1,2] and Philipp Mergenthaler[1]

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All multicellular organisms have evolved mechanisms to protect themselves against noxious stimuli such as substrate deprivation during a stroke. Preconditioning is a process where a noxious stimulus near to but below the threshold of injury is applied to the tissue and subsequently induces tolerance against stronger injury (Dirnagl *et al.*, 2003). The transcription factor hypoxia inducible factor 1 (HIF-1) is a major modulator regulating adaptive processes in response to changes in oxygen-homeostasis (Semenza, 2000). Among others, induction of HIF-1 activates the transcription of genes, which adapt the cellular metabolism to the reduced availability of oxygen. In this context, the expression of the glycolytic enzyme Hexokinase II is upregulated. In addition to performing the first obligatory step of glucose metabolism, increasing evidence suggests that Hexokinase II can also protect cells from apoptosis. We speculated that Hexokinase II exerts its antiapoptotic properties by interaction with other proteins in a multiprotein complex located at the mitochondrial outer membrane. To screen for putative interactors, we performed a membrane-based yeast-two hybrid screen using murine Hexokinase II as the bait and a mouse brain cDNA library as the prey. The screen yielded 108 positive clones that are currently further analysed. We are verifying the interaction of each candidate in a mammalian cell line and in primary brain cortical neurons as well as verifying neuronal expression of interactors. We present experimental strategies and functional properties of confirmed interactors.

The research leading to these results has received funding from the European Union's Seventh Framework Programme (FP7/2007-2013) under grant agreements n° 201024 and n° 202213 (European Stroke Network).

2 FUNCTIONAL CHARACTERIZATION OF THE RNA-BINDING PROTEINS FUS/TLS AND TARDBP/TDP-43

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The Fused in Sarcoma protein (FUS) and TAR DNA binding protein (TARDBP) are multifunctional proteins with structural and functional similarities. Both proteins are associated with different splicing factors and regulate transcription. Mutations in FUS are known to cause the neurodegenerative disease familial amyotrophic lateral sclerosis (ALS) type 6, whereas mutations in TARDBP can lead to familial and sporadic ALS.We are using a combination of different high-throughput approaches to elucidate the regulatory mechanism and function of these RNA-binding proteins. To identify RNA targets and exact binding sites of both proteins in HEK293 cells we are using a novel-crosslinking immunoprecipitation approach utilizing photoactivable ribonucleosides (PAR-CLIP) followed by deep-sequencing. Furthermore, we are investigating the contribution of FUS and TARDBP to gene expression by mRNA-sequencing and quantative proteomics of FUS- and TARDBP-knockdown cells.

3 A NOVEL METHOD FOR OPTI-MAL ESTIMATION OF CORTICO-MUSCULAR COHERENCE BASED ON MULTI-CHANNEL EEG/MEG RECORDINGS

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Cortico-muscular coherence (CMC) is an established method for the analysis of interactions between cortical and muscular activity. CMC can be studied noninvasively with millisecond precision using multi-channel electro- or magnetoencephalographic (EEG/MEG) recordings. However, previous EEG/

EMG studies on CMC were performed primarily either in sensor space, or using a Laplacian transform or employing beamformer techniques. Such approaches have two major limitations: 1) They do not guarantee finding optimal spatial filters for the detection of the strongest CMC, and 2) they can be associated with Type I errors due to the large number of electrodes/voxels used for the coherence estimation. Here, we propose a novel method, which provides an optimal solution for finding spatial filters and reduces chances of incorrect detection of cortico-muscular interactions. The core idea is to use multiple regression where narrowly filtered EEG signals serve as predictors and the electromyogram (EMG) serves as the dependent variable. Such approach, which we call Regression-CMC (R-CMC), allows an optimal detection of linear relationships between cortical and muscle activities. The regression coefficients serve as spatial filters and can be used to calculate the topography of cortical sources contributing to CMC. To avoid over-fitting we use Principal Component Analysis (PCA), thereby reducing the number of predictors entering the regression analysis. Our results demonstrated that a reliable estimation of CMC can be obtained with as little as 9-13 PCA components (reduction from original 96 EEG channels). For the evaluation of R-CMC approach we used data from isometric contraction of an index finger and were able to detect stable cortical patterns corresponding to tangential and radial sources in the contralateral sensorimotor cortical areas. Critically, the strength of the synchronization obtained with R-CMC was on average ~50% larger than that obtained with the conventional Laplacian transform. We suggest that R-CMC can be used as an effective approach for studying normal and pathological cortico-musclar interactions, e.g., in patients with stroke and Parkinson's disease.

Acknowledgement: ZB is supported by a CSB grant.

4 MICROCIRCUITRY IN THE MEDIAL ENTORHINAL CORTEX REVEALS A CELL-TYPE–SPECIFIC AND MODULAR ORGANIZATION

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Projection neurons in layer II (L2) of the medial entorhinal cortex (MEC) show place-specific responses in vivo that are organized in spatial hexagonal grids. MEC grid fields have been proposed to underlie the metric representation of external space. Anatomical studies and theoretical models of grid field activity suggest intralaminar recurrent connections, ascending interlaminar feedback connections, and the organization of ascending inputs in modules. Using scanning photostimulation, we investigate the functional microcircuitry of the two main projection neurons in L2 MEC, stellate and pyramidal cells. Our results reveal excitatory microcircuits with a cell-type–specific separation of intralaminar recurrent connections and ascending interlaminar feedback connections, and modular organization. Stellate cells display predominantly intralaminar recurrent connectivity; in contrast, pyramidal cells receive the majority of ascending interlaminar feedback connectivity from deep layers of the MEC, constituting the hippocampal feedback loop. Ascending interlaminar feedback connections to L2 are spatially organized in modules with distinct properties for the two cell types.

5 THE POSTSYNAPTIC 5-HT$_{1A}$-RECEPTOR AND THE EFFICACY OF ANTIDEPRESSANTS IN THE PORSOLT SWIM-TEST

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The central serotonergic (5-HT) system is implicated in the pathophysiology of depression. In clinical use selective serotonin reuptake inhibitors (SSRI) are combined with partial 5-HT$_{1A}$-receptor agonists to either gain an earlier onset or to augment antidepressant effects. However, it is not fully clarified how these effects are mediated by pre- and postsynaptic 5-HT$_{1A}$-receptors. In this study male and female wild-type mice as well as transgenic mice overexpressing the 5-HT$_{1A}$-receptor in outer cortical layers and hippocampus were investigated in the Porsolt swim-test (PST) and open field test (OFT). We examined the effects of the following antidepressants: the SSRI *citalopram*, the selective noradrenalin reuptake inhibitor *reboxetine*, the serotonin reuptake enhancer *tianeptine*, and the partial 5-HT$_{1A}$-agonists *buspirone* and *S15535*. Untreated male transgenic mice showed an antidepressant-like behaviour in the PST compared to wild-type mice. Drug testing in the PST revealed that *citalopram* (5.0 and 10.0 mg/kg) produced only in transgenic mice an antidepressant-like effect without affecting locomotor activity. *Reboxetine* (20 mg/kg) had no antidepressant-like effect except for female wild-type mice. Likewise, *tianeptine* (20 mg/kg) produced only in male wild-type mice an antidepressant-like effect. The two partial 5-HT$_{1A}$-receptor agonists had a weak effect in the PST: *S15535* affected swimming behaviour in none of the four groups, whereas the high dose of *buspirone* (3 mg/kg) increased the immobility time

only in male wild-type mice. However, this effect interfered with a lower motor activity. In summary, the antidepressant-like phenotype of untreated male transgenic mice accounts for an involvement of postsynaptic 5-HT_{1A}-receptors in the onset of depression. Moreover, it seems likely that the antidepressant effect of *citalopram* is partly mediated by postsynaptic 5-HT_{1A}-receptors. Our findings also suggest that partial 5-HT_{1A}-receptor agonists given alone do not act as antidepressants in the PST.

6 IMPROVING OPTICAL COHERENCE TOMOGRAPHY SENSI-TIVITY AND SPECIFICITY IN MULTIPLE SCLEROSIS BY ANALYSIS OF RETINAL NERVE FIBER LAYER SHAPE

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OBJECTIVE: To evaluate shape based Retinal Nerve Fiber Layer (RNFL) parameters in addition to conventional thickness parameters to enhance sensitivity and specificity of Optical Coherence Tomography (OCT) in Multiple Sclerosis. BACKGROUND: OCT promises a potential role in Multiple Sclerosis diagnostics. However, its current value is limited due to low sensitivity/specificity and high noise/signal ratio of time domain OCT. METHODS: We compared RNFLT measurements from Multiple Sclerosis eyes (n=217) with measurements from healthy controls (n=306). Next to RNFL average thickness, quadrant thicknesses and clock hour thicknesses a total of 199 shape attributes were calculated using a combination of analytical and stochastic methods. Naïve Bayes algorithms, linear and polynomial Support Vector machines were trained in different combinations using thickness and shape attributes. Effectiveness of these models in classifying between healthy and Multiple Sclerosis eyes was analyzed with receiver operating characteristic curves (ROC). RESULTS: On all data, average RNFL thickness was the most effective single-attribute classifier between healthy and Multiple Sclerosis eyes (AUC=0.733). Using the device's normative database, eyes were classified with a sensitivity of 20% and a specificity of 98%. The most effective shape and thickness using model based on linear support vector machines achieved 43% sensitivity at 98% specificity (AUC=0.790) When only thickness parameters were used , a similar model only showed 32% sensitivity at 98% specificity (AUC=0.818, $p<0.001$). CONCLUSION: Using machine learning models and RNFL shape in addition to thickness parameters can improve classification efficiency between healthy and Multiple Sclerosis eyes. When these approaches are further developed in spectral domain OCT results with lower noise and higher RNFL steadiness, a substantial step towards clinical usage of OCT in Multiple Sclerosis seems feasible.

7 NEUROD FAMILY TRANSCRIP-TION FACTORS *NEX* AND *NDRF* REGULATE NEOCORTICAL REMOTE AXOGENESIS

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Establishment of long-range fiber tracts by neocortical projection neurons is fundamental for higher brain functions. The molecular control of axon tract formation, however, is still poorly understood. Here, we have identified basic helix-loop-helix (bHLH) transcription factors *NEX* (*Neurod6*) and *NDRF* (*Neurod2*) as key regulators of fasciculation and targeted axogenesis in the neocortex. In *NEX/NDRF* double mutants, fiber tracts of neocortical origin are massively reduced or completely absent. Callosal axons, which are most severely affected, lack expression of the cell adhesion molecule contactin 2, defasciculate in the subventricular zone, and follow random trajectories within the ipsilateral cortex instead of crossing the midline. In contrast to long-range axogenesis, generation and maintenance of pyramidal neurons, initial axon outgrowth, dendritogenesis, and glutamatergic synapse assembly are largely unaffected, and thus under distinct transcriptional control. These findings demonstrate that neocortical projection neurons require transcriptional specification by neuronal bHLH proteins to execute an intrinsic program of remote connectivity.

Support: DFG Research Center, Molecular Physiology of the Brain (CMBP), ; DFG Excellence Cluster NeuroCure (Exc 257).

8 HIGH CONTENT MICROSCOPY ON NOCICEPTIVE NEURONS

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The cellular mechanisms leading to pain sensitization remain fragmentary. One known component involved in various sensitization models is the epsilon

isoform of protein kinase C (PKCå). Activation of PKCå is restricted to a distinct population (15-25 %) of DRG-neurons. In a first step these neurons have been defined to be a subgroup of the class of IB4-positive nociceptive neurons. We attempted to further characterize this subgroup. Current subgroup identification is largely based on experimentator-based evaluation of immunfluorescence or in situ hybridisation techniques. An arbitrary and not even by the single experimentator clearly definable threshold is set mentally. But our eye is very much dependent on the local surrounding signals in judging intensities. Thus this technique is inherently inaccurate. In contrast, we use a quantitative software based evaluation method using among others the Cellomics High Content Screening microscope ArrayVTI. Thereby we correlate functional aspects such as PKCå activatability with other aspects of importance in nociception such as subgroup marker expression (TRPV1, CGRP, IB4), as well as Calcium influx characteristic. We corroborate the expression studies by a single molecule in situ hybridisation.

9 EFFECTS OF CORTICOSTERONE ON HIPPOCAMPAL GAMMA OSCILLATIONS

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Acute stress triggers the release of variable amount of steroid hormones, such as corticosterone (CORT), which alters neuronal functions in a time-dependent manner. CORT can bind to high affinity mineralocorticoid receptors (MR), which are mainly expressed in limbic regions, or to low affinity glucocorticoid receptors (GR) which have a broader distribution in the brain. Increase of corticosteroid hormones to high levels have been shown to interfere with hippocampus-dependent memory formation both in rodents and humans. Moreover, recent studies provide evidence that CORT has opposite effects on synaptic plasticity in ventral versus dorsal hippocampus, but very little is known about the impact of stress hormones on hippocampal oscillations, which have been implicated in the formation and consolidation of declarative and spatial memory. One of these network oscillations, gamma oscillations, can be studied under in vitro conditions by application of different drugs (kainate, carbachol or acetylcholine -ACh-) or by tetanic stimulation of afferent fibers. We examined the effects of CORT on gamma oscillations either induced by 10 μM ACh co-applied with 2 μM ACh esterase inhibitor physostigmine in the CA3, or by tetanic stimulation of Schaffer collaterals in the CA1 of ventral hippocampal rat slices. Preliminary results suggest that application of CORT (1 μM) causes a mild augmentation in the power of both types of gamma oscillations, with no main effect on the mean gamma frequency. Our next goal is to determine the contribution of different types of corticoid receptors (GR vs. MR) to such oscillations.

10 INVESTIGATION OF THE FRACTALKINE RECEPTOR CX3CR1 AS A DIAGNOSTIC MARKER OF MULTIPLE SCLEROSIS

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Multiple sclerosis (MS) is a demyelinating autoimmune disease of the central nervous system (CNS). Its clinical course and symptoms present a large variability, for which clear diagnostic parameters are lacking. Fractalkine is a chemokine involved in leucocyte chemotaxis and activation. Previous data from gene expression and flow cytometry studies demonstrated a significantly lower expression of the fractalkine receptor CX3CR1 of natural killer (NK) cells in MS patients compared with healthy individuals. Thus, disease activity appears to be significantly correlated with the expression of CX3CR1. Our objective is now to investigate possible association between CX3CR1 two variants V249L and T280M and MS susceptibility.. Genotyping of single nucleotide polymorphisms (SNPs) rs3732379 (V249L) and rs3732378 (T280M) has been performed in independent, well-defined cohorts of 600 MS patients and 600 healthy controls. These genotypes are additionally analyzed in correlation with the disease phenotype, disability measures, and age at onset of MS patients. Thus, apart from the possible association of the SNPs with disease susceptibility, analyses of screening results and their correlations to the disease severity allow us to determine whether these variants may represent a biomarker of degree of MS severity. Here, we present results of the genotyping and association analyses.

Supported by a grant awarded under the 7th Framework Programme (FR7).

11 DENDRITIC SPINE: A KEY ROLE OF PRG-5

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Dendritic spines are the primary recipients of excitatory input in the central nervous system. They provide contacts between somata, axons and dendrites. In dissociated cultures of hippocampal neurons, dendritic spines are detected starting from the seventh day in vitro (d.i.v. 7), according to developmental age, level and direction of synaptic activity. Here we dissect the roles of the Plasticity-related gene 5 (PRG-5), a multi spanning membrane

protein, member of the vertebrate-specific PRG family, that localizes and promotes the induction of spine in primary neurons, cultivated between d.i.v. 1 and d.i.v.3. Deletion experiments underline C-terminus as the most important region for the induction of spine. These data suggest that PRG-5 may be control, as a receptor, the spine induction in primary neurons. *Supported by a grant of the NäFoG and Sonnerfeld Stiftung.*

12 THE LET-7 MIRNA AS CENTRAL REGULATOR OF STEM CELL COMMITMENT

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miRNAs are small, non-coding RNAs with a global influence on the proteome. miRNAs regulate fundamental processes such as early development, cell specification, growth control and apoptosis, but also higher order functions in the CNS such as synaptic plasticity and memory formation. We are studying the role of the let-7 miRNA, a crucial regulator of stem cell self-renewal and neural commitment. Let-7 regulates two novel pluripotency genes, *Lin28* and *Lin41*. We recently assigned molecular functions to both Lin28 and Lin41, defining Lin28 as a let-7 specific RNA binding protein that inhibits functional maturation of let-7 by the Dicer ribonuclease. These results provide a mechanistic understanding of the oncogenic activity of Lin28 and the ability of Lin28 to promote pluripotency in somatic cells. Lin41 is a Trim family E3 ubiquitin ligase and the founding member of the Trim-NHL subfamily of developmental regulators. Inactivation of Lin41 in gene trap mice results in defective neural tube closure, a phenotype currently under study in our lab. We are generating a conditional allele, to allow functional analysis of Lin41 in adult neurogenic zones. We describe Lin41 localization to P-bodies and physical interaction with the essential miRNA pathway protein Ago2. Lin41 regulates Ago2 turnover and is therefore a repressor of miRNA-mediated silencing. We present a model for Trim-NHL proteins as a molecular switch: sequentially inhibiting and activating miRNA circuitry in stem cells.

13 NEURONAL CHLORIDE TRANSPORT IN HUMAN AND RAT NEOCORTEX

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Two contending mechanisms, a reduced outward (*via* KCC2) or increased inward (*via* NKCC1) Cl^- transport have been proposed to underlie depolarizing $GABA_A$ responses in human epileptogenic tissues. We investigated the properties of Cl^- transport in human and rat neocortical neurones using intracellular recordings (layer II/III) in slices of cortical tissue. Pharmacologically isolated $GABA_A$ receptor-mediated inhibitory postsynaptic potentials ($IPSP_A$) were used to estimate the ionic gradient. The kinetic of Cl^- efflux after injections was determined before and during the application of selected blockers of Cl^- routes (furosemide, bumetanide, 9AC and Cs^+). Human neurones exhibited a fairly depolarized reversal potential of $IPSP_A$ (E_{IPSP-A}) of -61.9±8.3 mV; in half of the neurones E_{IPSP-A} averaged -68.6±2.3 mV, in the others -55.2±5.7 mV (rat neurones: -68.9±2.6 mV). In human neurones, $IPSP_A$ recovered from Cl^- loads with an average tau of 19.1±9.8 s (rat neurones: 7.0±2.3 s). From the tau values obtained in the different experimental conditions we calculated rates of Cl^- extrusion (1/tau) *via* individual routes of Cl^-, revealing that KCC2 comprises 51.5 % of total rate in rat neurones. In human neurones, the total rate of Cl^- extrusion was 64.4 % smaller, the rates *via* KCC2, NKCC1 and ClC were smaller by 81 %, 61 % and 85 %, respectively than in rat neurones. The rate *via* AE in human neurones was 103 % larger than in rat neurones. We propose, 1) KCC2 is the dominating component of Cl^- extrusion in healthy cortical neurones 2) reductions of KCC2, rather than upregulated NKCC1, contribute to depolarized E_{IPSP-A} of human epileptogenic cortex.

14 FUNCTIONAL ASSESSMENT OF MICROGLIA IN HOMEOSTASIS USING A CD11B-HSVTK TRANSGENIC MOUSE MODEL

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Recent findings point towards a greater need to understand the highly versatile state of microglia in the absence of disease and their contribution to central nervous system (CNS) homeostasis. In order to address this question, we use a CD11b-promoter driven herpes simplex virus thymidine kinase (HSVTK) transgenic mouse model for selective ablation of microglial cells upon the treatment of ganciclovir (GCV). GCV delivery directly into the CNS by miniosmotic pumps results in a selective ablation of > 90% of resident microglia without disturbing peripheral (systemic) CD11b cells. Initial results reveal that *in vivo* microglia-depleted brains exhibit unique electrophysiological responses when compared to control groups. We conclude that this protocol is efficient in assessing first parameters for possible alterations in neuronal circuitry.

15 EFFECTS OF HISTAMINE ANTAGONISTS AND POTASSIUM CHANNELS BLOCKERS ON GAMMA OSCILLATIONS

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The aim of our study is to test the effect of H1 histamine receptors antagonist and potassium channels Kv 11.1 blocker on gamma oscillations. Those drugs could play a role in the treatment of cognitive impairment and dementia, since gamma oscillations may promote binding and storage of information. Experiment were performed in horizontal hippocampal slices obtained from brain of young adult Wistar rats (160-180 g). Gamma oscillations were extracellulary recorded from "stratum pyramidale" of area CA3 and CA1. Kainic acid (0.1 μM) or acetylcholine (10 μM) + physostigmine (2 μM) were used to induce gamma oscillations. Astemizole, a histamine H1 receptors antagonist and Kv 11.1 blocker, at a concentration of 5 μM, significantly increased the power of kainate-induced gamma oscillations by about 40%. In order to understand whether this increase is due to the block of H1 receptors or Kv channels we tested fexofenadine (H1 blocker) at a concentration of 10 μM, and sertindole (Kv 11.1 blocker) at a concentration of 5 μM. Both blockers did not change significantly the power of kainate-induced gamma oscillations. Surprising results were found when gamma oscillations were induced by acetylcholine. In this case both fexofenadine and sertindole significantly increased the power of gamma oscillations. Moreover, the increase induced by astemizole of this type of gamma oscillations was up to 10 times more than the control. The result indicate that the block of both histaminergic H1 receptors and Kv channels affect the power of gamma oscillations. This effect is present when gamma oscillations are induced with acetylcholine 10 μM plus physostigmine 2 μM. The power of kainate-induced gamma oscillations was significantly increased only by astemizole, that simultaneously blocks H1 receptors and Kv channels.

16 CAPILLARY PERICYTES DO NOT MEDIATE FUNCTIONAL HYPEREMIA DURING BICUCULLINE-INDUCED NEURONAL ACTIVITY BURSTS

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Adaptation of cerebral blood flow to local increases in neuronal activity guarantees spatially and temporally matched supply of substrates. This 'neurovascular coupling' underlies non-invasive brain mapping techniques. The spatial acuity of these techniques depends ultimately on the disposition of blood flow regulating elements. Evidence obtained in brain slices indicated that pericytes in capillaries might mediate neurovascular coupling. However, their role *in vivo* remains unexplored. We have used intravital two-photon microscopy to study pericytes and the dynamic changes of vessel diameter and red blood cell (RBC) velocity during neuronal activity increases. We induced sharp recurring bursts of neuronal activity by inserting a micropipette filled with bicuculline, a $GABA_A$ receptor antagonist, in the cortex of 8 mice. Pial, penetrating and precapillary arterioles were imaged together with layer II pericyte-containing capillaries. RBC velocity increases were detected in all vessel types. Diameter responses of pial, penetrating and parenchymal arterioles peaked at 102.4±3.3%, 103.4±3.5%, and 102.3±5% of pre-burst basal values, respectively. Capillary diameter responses reached only 100.1±2.5% of pre-burst basal values at the time of maximal RBC velocity increases. Our data suggest that pial, precapillary and penetrating arterioles are responsible for the blood flow increase induced by neural activity, and the distribution of these, but not of pericytes in capillaries, will dictate the spatial resolution of the functional hyperemia which underlie functional imaging techniques.

Supported by the DFG, the BMBF and the Hermann and Lilly Schilling Foundation.

17 MIR-128: A PLEIOTROPIC REGULATOR OF NEURONAL TRANSLATION

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microRNAs (miRNA) are a large class of non-coding RNA important in the regulation of the proteome mainly through silencing and/or degradation of mRNA. Over 400 miRNA genes have been annotated, they are expressed and function in all cells as regulators of many cellular processes. Several highly tissue specific miRNAs are known to coordinate cell-specific gene expression programs during development. miR-128 is one of a small group of brain enriched, neuron-specific miRNAs. There is evidence for misregulation of miR-128 in glioma and neuroblastoma as well as other malignancies, but functional characterization of miR-128 in CNS development and function is only beginning. Like the paradigm neuronal miRNA, miR-124, miR-128 is not expressed in radial progenitors but is induced upon neuronal differentiation. Deep sequencing of synaptosomal miRNA revealed high levels of miR-128. Consistent with this expression pattern, we have identified and verified several target mRNAs for miR-

128 that are subject to direct translational repression. miR-128 target gene interactions are likely to influence development (Doublecortin, FoxP2, Reelin), growth control (Aff4, Casc3, Phf6) and activity (Adora2a, Adora2b, Creb1, RpsKa5, Slc6a1/GAT1). To further investigate regulatory interactions under the control of miR-128, we are performing gain- and loss-of-function experiments by electroporation *in ovo* in the spinal cord and *in utero* in the mouse cortex. Preliminary results of these experiments will be presented.

18 DISTINCT MUSCARINIC ACETYLCHOLINE RECEPTOR SUBTYPES MEDIATE PRE- AND POST-SYNAPTIC EFFECTS IN RAT NEOCORTEX

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Cholinergic transmission is implicated in learning, memory and cognition. However, the cellular effects induced by activation of the different subtypes of muscarinic acetylcholine receptors (mAChR) are poorly understood. We investigated the effects of the cholinergic agonist carbachol (CCh) and various mAChR antagonists on neuronal activity in rat neocortical slices using intracellular and field potential recordings. CCh increased neuronal firing, but reduced synaptic transmission and the paired-pulse depression. The increase of neuronal firing was mediated by M_1 mAChR since it was antagonized by pirenzepine (M_1/M_4 mAChR antagonist) but not by AF-DX 116 (M_2/M_4 mAChR antagonist). Both antagonists were capable to fully reverse and prevent the depressant effect of CCh on synaptic transmission suggesting that this synaptic depression was mediated by M_4 mAChR activation. CCh also decreased the paired-pulse inhibition of field potentials *via* activation of M_2 mAChR, since this effect was strongly antagonized by AF-DX 116 or atropine but marginally by pirenzepine. Finally, the M-current blocker linopirdine, mimicked the action of CCh on neuronal firing. However, linopirdine had no effect on the amplitude of postsynaptic potentials (PSP) or the paired-pulse ratio, indicating that M-currents are only involved in the increase of neuronal firing but not in the depression of PSPs or paired-pulse inhibition. The dual effects of mAChRs activation in the neocortex, namely a depression of PSP and an increased neuronal firing would tend to decrease synaptic "noise" and concomitantly increase neuronal responsiveness. Together, the two effects would improve the filtering capabilities and may represent a basis of "neuronal attention".

19 A NEW APPROACH TO SPINAL CORD INJURY LESIONS

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After spinal cord injury (SCI), primary and secondary damage occur due to several endogenous processes including inflammation and the development of a glial scar. So far many different approaches have been tried to boost regeneration, axonal regrowth and sprouting, including enhancing or decreasing endogenous processes, the injection of cells and the use of polymeric devices in mice after SCI. We are introducing a new technique with a tissue graft ($1mm^3$) extracted from the subventricular zone (SVZ), to give neurons an orientation matrix to grow in a specific direction. Through the use of green fluorescent protein (GFP) expressing mice under the â-actin promoter as donor mice, we can easily distinguish donor from host neurons and cells. 20 mice underwent SCI at the Th7 level, receiving either SVZ grafts or cortex grafts. After 14 days the mice were sacrificed and 20μm sections cut on a cryostat. Using immunhistochemical techniques the survival of the grafted cells, axonal regrowth, newly established connections and the size of the glial scar was counted and measured. We found GFP expressing neurons, astrocytes and blood vessels in and around the lesion scar. Some axons extend over the scar growing into the caudal spinal column. In the control group, we could distinguish astrocytes and blood vessels, but only seldom neurons. Behavioral tests showed a slightly better outcome of the experimental group, which was not statistically significant. We present a new technique that allows the stable monitoring of the fate of a transplanted tissue graft, derived from the subventricular zone, allowing us now to further study the role of this tissue graft in the regulation of endogenous regenerative processes. We hope to find some new ways to overcome some of the detrimentally effects of SCI.

20 ACUTE AND LONG-TERM NEUROPLASTICITY WITHIN THE CENTRAL AUDITORY PATHWAY AFTER NOISE-INDUCED HEARING LOSS

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Noise exposure leads beside cochlear hair cell loss to 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 (deprivation) and neuronal changes directly related to the auditory overstimulation. For the understanding of noise induced functional disabilities, it seems to be highly important to clarify the influence of these two mechanisms. While hair cell loss and therefore deafferentiation appears slowly in the early days after treatment, it should be possible to study effects on central auditory structures at different stages after an acoustic overstimulation. In this study, normal hearing mice were noise-exposed (3h, 115 dB SPL, white band noise 5-20 kHz) under anaesthesia. Before and after the noise exposure as well as one week later, hearing thresholds were determined by measurements of the frequency specific auditory brainstem response. Neuronal activity was investigated in auditory structures in-vivo with manganese enhanced MRI (to monitor calcium dependent synaptic activity). In addition, cell densities were determined in these areas to identify a modified cytoarchitecture. The results clearly demonstrate that acoustic overstimulation directly influences the physiology and anatomy in the neural network within the central auditory pathway. Whereas acute noise exposure only affects the lower auditory pathway, long-term effects could also be observed in higher auditory structures.

21 PROPERTIES OF GABAERGIC INTERNEURONS IN SUPERFICIAL LAYERS OF THE ENTORHINAL CORTEX

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The entorhinal cortex (EC) occupies a pivotal position in gating hippocampal input and output. This structure receives input from the neocortex and medial septum and projects to the CA3 region via DG or directly to the CA1 region of the hippocampus. The EC shows oscillatory activity in the theta and gamma frequency band, which are important in cortical information processing. Although there is compelling evidence that interneurons are involved in generation of rhythmic network activity, little is know about the properties of entorhinal cortex interneurons and their role in network oscillations. Our aim was to study the morphological and electrophysiological properties of interneurons in the medial EC. Whole-cell patch-clamp recordings in current and voltage clamp modes were obtained from interneurons of superficial layers (II/III) of the medial EC. We found that interneurons in superficial layers of the EC form morphologically and electrophysiologically heterogeneous groups with different intrinsic and firing properties. The most of recorded interneurons were regular spiking cells (at about 70% of all recorded cells). In addition, we have found only a small number (~10%) of non-adapting "stuttering" parvalbumin-positive interneurons. In contrast to locally distributed "regular" spiking interneurons, these GABAergic cells demonstrate horizontally distributed large-scale axonal arborisation within the superficial layers. We suggest that interneurons with different morphological and electrophysiological properties are differentially involved in network oscillatory activity of the EC.

Supported by the FP6 (EPICURE) to T.G.

22 EXPRESSION OF CX3CR1 IS ASSOCIATED WITH DISTINCT PHENOTYPICAL AND FUNCTIONAL CHARACTERISTICS OF NK CELLS

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We previously demonstrated a reduced expression of the chemokine receptor CX3CR1 on natural killer (NK) cells in patients with Multiple Sclerosis (MS) compared to healthy individuals and found a correlation between CX3CR1-expressing NK cells and disease activity in MS patients. We also showed that an increased cytotoxic activity of NK cells was associated with a higher CX3CR1 expression. Here, we aim to elucidate whether the expression of CX3CR1 discriminates between two distinct subtypes of NK cells by analysing phenotype and effector functions of CX3CR1+ vs. CX3CR1- NK cells. Our data show different cytokine pattern of CX3CR1+ and CX3CR1- NK cells, while IFN-gamma expression was comparable in both NK cell subsets, $CX3CR1^{neg/low}$ NK cells expressed higher amounts of TNF-alpha and GM-CSF, elevated levels of anti-inflammatory and Th2-like cytokines IL-10, IL-13 and IL-5 and exert a stronger proliferative response to IL-2 in comparison to their $CX3CR1^{high}$ counterparts. In addition, we show that CX3CR1+ and CX3CR1- NK cells differently influence monocytes, since only $CX3CR1^{neg/low}$ NK cells induces an increased expression of the costimulatory molecule CD40. Although $CX3CR1^{high}$ and $CX3CR1^{neg/low}$ NK cells present many similarities with $CD56^{dim}$ and $CD56^{bright}$ subsets, respectively, we show that $CX3CR1^{neg/low}$ NK cells not only consist of $CD56^{bright}$ but also up to 60% of $CD56^{dim}$ NK cells. Finally, we show that most cytokines promoting activation/proliferation of NK cells induce downregulation of CX3CR1 expression. Altogether, our findings support the assumption of plasticity of NK cell function and of their ability to contribute both, amplifying and terminating the inflammatory reaction.

23 GP130-DEPENDENT ASTROGLIOSIS AND ASTOCYTE SURVIVAL IS CRUCIAL FOR CONTROL OF TOXOPLASMA ENCEPHALITIS AND EXPERIMENTALLY INDUCED AUTOIMMUNE ENCEPHALOMYELITIS

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In various CNS pathologies there is robust astrocyte activation; however their *in vivo* function is largely unknown. To study the role of astrocytes in *Toxoplasma* Encephalitis (TE) and experimentally induced autoimmune encephalomyelitis (EAE), we generated mice deficient in astrocyte specific expression of gp130, the signal transducing receptor for cytokines of the IL-6 family. In TE, GFAP+ astrocytes of gp130fl/fl control mice were activated, increased in number and effectively contained inflammatory lesions and parasites resulting in survival of TE. In contrast, infected GFAP-Cre gp130fl/fl mice lost GFAP+ astrocytes in inflammatory lesions resulting in an inefficient containment of inflammatory lesions, impaired parasite control and a lethal necrotizing TE despite normal intracerebral production of chemokines, cytokines, antiparasitic effector molecules, and recruitment of leukocytes. *In vitro*, infection of astrocytes with *T. gondii* and stimulation with LPS or TNF significantly increased apoptosis of GFAPCre gp130fl/fl astrocytes. In addition, numbers of GFAP+ astrocytes were strongly reduced in experimental autoimmune encephalomyelitis (EAE) of GFAP-Cre gp130fl/fl mice due to enhanced apoptosis. Consequently, both clinically and histopathologically, these animals were characterized by a significantly more severe EAE and finally succumbed to chronic EAE, whereas control mice recovered. In contrast to control mice, intracerebral T cells did not become apoptotic and persisted in EAE of GFAP-Cre gp130fl/fl mice. Furthermore, we generated mice with astrocyte-specific gp130 signal cascade deficiency in either Stat1/3 or ERK pathway. Induction of EAE in these mice suggested that prevention of astrocyte apoptosis, restriction of demyelination and T cell infiltration were dependent on the astrocytic gp130-SHP2/Ras/ERK but not on the gp130-Stat1/3 pathway demonstrating that astrogliosis is crucial to ameliorate EAE. Thus, gp130-dependent survival of astrocytes is of crucial importance in TE and EAE.

24 THE ROLE OF Á-1,2-MANNOSIDASE IN REGULATION OF CENTRAL NERVOUS SYSTEM INFLAMMATION

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Cell surface glycans play an important role in regulating immune responses, and are implicated in inflammatory diseases. The glycosidase á-1,2-mannosidase removes mannose residues in the process of protein n-glycosylation, initiating a shift from high-mannose glycans to complex glycans, a shift that seems to be crucial for the discrimination of self from non-self antigens. Previously, we showed that á-1,2-mannosidase was decreased in patients with multiple sclerosis (MS) that responded well to immunomodulatory therapy. On the other hand, in transplantation, blockade of á-1,2-mannosidase inhibits allograft rejection, indicating that glycosidase inhibition may have anti-inflammatory effects also in neuroinflammation. To prove this, we applied Kifunensine (KIF), a potent inhibitor of á-1,2-mannosidase, to mice suffering from experimental autoimmune encephalomyelitis (EAE), an animal model of MS. We show that, in vivo, administration of KIF had a biological effect on dendritic cells (DC) and T cells as indicated by significant downregulation of complex glycans and an upregulation of high-mannose glycans. Further, we show that, unexpectedly, administration of KIF intraperitoneally during the induction phase of EAE led to a significant EAE exacerbation. However, when KIF was administered at the peak of disease no effect was observed. Thus, we hypothesise that á-1,2-mannosidase inhibition may affect DC by enhancing their priming capacity or/and perhaps diminishing their potential to induce immune regulation. To explore this, we examined markers associated with antigen presentation and chemotaxis on DC treated in vitro with the á-1,2-mannosidase inhibitor. Preliminary data show that KIF treatment did not significantly affect expression of these molecules in DC generated in vitro. Work in progress is extending this analysis to different DC subsets analysed after in vivo KIF application.

This study is supported by a grant of the DFG (SFB650)

25 PARACELLULAR TRANSPORT OF AS006 - A NOVEL PAIN RELIEVING DRUG - IS AUGMENTED BY THE ABSORPTION ENHANCER CHITOSAN

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In a series of models for acute and chronic inflammatory pain, the new morphine derivate AS006 (AlcaSynn GmbH, Austria), has been shown to have excellent efficacy. The activation of central μ-opioid receptors is associated with adverse actions, including respiratory depression, sedation and physical dependence. In contrast, AS006 is an effective opioid analgesic which should not cross the blood brain barrier and selectively activates peripheral opioid receptors on sensory neurons in injured tissues. Therefore, AS006 is of high interest to be administered orally. To increase the oral bioavailability of AS006 we used the absorption enhancer chitosan. Human colon epithelial cells were grown on permeable supports until confluency and mounted in Ussing chambers for measurement of transepithelial resistance and apical-to-serosal flux of AS006. A liquid chromatography-tandem mass spectrometry method was developed and validated for quantification of AS006 in HEPES buffered samples taken from the basolateral side of the epithelial cell layers. Chitosan induced a marked and consistent drop of transepithelial resistance (R^t) via interaction with the tight junctions. Flux measurements revealed an increased permeability for AS006, indicating an increased paracellular passage of AS006. In vitro measurements suggest AS006 as a promising analgesic for targeted activation of peripheral opioid receptors, which can cross the epithelial cell barrier when co-applied with the absorption enhancer chitosan.

26 BILATERAL EFFECTS OF UNILATERAL INTRA-COCHLEAR ELECTRICAL STIMULATION ON THE CENTRAL AUDITORY PATHWAY

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The present study investigates the microstructural and neurophysiological consequences of unilateral chronic intracochlear electrical stimulation within the ascending auditory pathway at the cellular level. A cochlear implant was implanted in normally hearing guinea pigs. The first 4 electrode contacts are being used to stimulate the cochlear nerve fibers within the first turn of the cochlea. Six weeks after surgery the stimulation of the implanted animals started. The animals of the experimental group were stimulated for 90 days. Both experimental and control group (implanted but not stimulated) experienced a similar daily acoustic environment (16 hours). Animals of the experimental group showed a significantly lower average spontaneous activity on both sides of the cochlear nucleus (CN) and auditory cortex (AC) than the controls. In the inferior colliculus (IC) and medial geniculate body (MGB) only the side was affected which receives direct afferent input from the non-implanted side. The neuronal cell density of the CN was significantly higher on the stimulated side compared to the corresponding side of the controls. The opposite applies to the non-stimulated side. In the MGB, IC and the AC, conservation of the neuronal structure was observed bilaterally upon electrical stimulation. The bilateral changes at the cellular level were accompanied by a slight hearing loss on the non-implanted side. The present findings indicate a neuronal plasticity to balance the input of simultaneous electrical and acoustical stimulation. The results of this study might be of importance when considering cochlear implantation for patients with single-sided deafness. They may also improve our understanding of the highly variable clinical course of auditory rehabilitation observed frequently after sequential, bilateral cochlear implantation.

27 A MODEL FOR INHERITANCE OF HIPPOCAMPAL PHASE PRECESSION: FROM CA3 TO CA1

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

28 SPINAL CORD – MOTOR CORTEX CO-CULTURE MODEL: A NEW TECHNIQUE TO STUDY NEURONAL REGENERATION *IN VITRO*

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Today several hippocampal as well as spinal in vitro lesion models are used to investigate neuronal differentiation, axonal growth and path finding. We report here for the first time a new slice co-culture model for the study of neuronal regeneration. Spinal cord (sc) from postnatal (P1-P2) C57black6 mice and motor cortex (mc) dissected from postnatal (P1-P2) mice expressing green fluorescent protein (GFP) under the control of the â-actin promoter were chopped either in a sagittal longitudinal plane for the sc or in a coronal plane for the mc. Afterwards the medial cortex zone was orientated to the rostral end of the spinal cord, placed either directly next to it or at a distance of 10 mm, mounted with collagen and incubated up to two weeks. Through the use of GFP expressing mice as mc donors we could easily distinguish ingrowing mc neurons and astrozytes from the nonfluorescent wildtype sc neurons. Furthermore axonal regrowth and newly established connections were analysed via confocal microscopy after immunhistochemical staining. We found a strong ingrowth with growth cones, reestablishment of cortical fibers and new synaptic connections from the mc slices into the spinal cord slices, especially when placed directly next to each other. This new slice co-culture model provides an important tool for a variety of questions in the field of neuronal regeneration *in vitro*

29 DISSECTING DYNAMIC CHAN-GES IN NEOGENESIS OF ADULT GRANULE NEURONS – A QUANTITATIVE APPROACH

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Adult hippocampal neurogenesis originates from precursor cells in the adult dentate gyrus and results in new granule cell neurons. A model of this development has been established before, but the exact dynamics of neuronal development in the dentate gyrus are unknown. To analyze the temporal pattern of adult hippocampal neurogenesis and quantify the development we have used transgenic mice expressing green fluorescent protein (GFP) under the nestin promoter and analyzed the relative number of type-1, type-2, type-3, early postmitotic cells and newly generated granule cells at different time points after BrdU injection. Additionally we determined the changes in absolute numbers of BrdU-positive, Nestin-GFP-positive, and Doublecortin-positive cells over time. We found an increase in BrdU-positive cells within 48 hours after BrdU injection. Between 48 hours and 21 days the absolute number of BrdU-positive cells decreased again. These data lead to the conclusion that the BrdU-labeled cohort of cells is highly proliferative within the first 48 hours followed by a prolonged phase of selective cell death. Irrespective of this, the extensive data confirm the previous model but indicate that within one cohort of labeled cells the peak number is reached after 2 instead of after 3 days.

This study was funded by Volkswagen Stiftung.

30 DIFFERENTIAL MODULATION OF GAMMA OSCILLATIONS VIA ATP-ACTIVATED P2X AND P2Y RECEPTORS IN THE RAT HIPPOCAMPUS

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ATP is the primary energy source within cells and also an extracellular signalling molecule released e.g. by neurons and glial cells. Functional ionotropic (P2X) and metabotropic (P2Y) ATP receptors have been described on hippocampal interneurons and astrocytes, however their role in network activity is yet to be elucidated. Here, we investigated the role of ATP and its receptors on gamma network activity. After preparing acute hippocampal slices of the rat brain we induced gamma oscillations (30-90 Hz) in the CA3 region by using either acetylcholine (ACh) or kainic acid (KA). Extracellularly applied ATP reduced the power of both ACh- and KA-induced oscillations in a concentration dependent manner. PPADS, a broad spectrum ATP receptor antagonist, increased the power of ACh-, but not of KA-induced network activity. Subsequently we applied MRS 2179 and TNP-ATP to selectively inhibit P2Y1 and P2X1/P2X2 receptors, respectively. We found that ionotropic P2X receptors reduce while metabotropic P2Y1 receptors enhance gamma power. Moreover, TNP-ATP significantly inhibited the peak autocorrelation coefficient and lowered the frequency of the gamma oscillations indicating that P2X1/P2X2 receptors increase peak autocorrelation and increase

the gammthe frequency of a oscillations. In conclusion our results imply that ACh- and KA-induced gamma oscillations involve different neuronal pathways modulated differently by ATP. The activation of P2Y and P2X receptors appear to have distinct modulatory effects on hippocampal network activity.

31 NEURODEGENERATION AND LOSS OF SYNAPTOTAGMIN 1 IN MICE DEFICIENT FOR THE ENDOCYTIC SORTING ADAPTOR STONIN 2

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The maintenance of synaptic transmission depends on the biogenesis and recycling of presynaptic vesicles (SVs), specialized organelles that store and secrete non-peptide neurotransmitters. Several modes of retrieval of SV membranes have been proposed to operate at the synapse. These include kiss-and-run exo-endocytosis, bulk internalization of membrane, and clathrin-mediated endocytosis. While many constitutively internalized cargo proteins are recognized directly by the clathrin adaptor complex AP-2, stimulation-dependent endocytosis of membrane proteins is often facilitated by specialized sorting adaptors. Recently, we identified stonin 2, a mammalian ortholog of *Drosophila* stoned B, as an AP-2-dependent sorting adaptor dedicated to the internalization and recycling of synaptotagmin, a function that appears to be evolutionary conserved from worms to mammals. However, the consequences of stonin 2 loss-of-function at the organismic level have not been studied in mammals. We report here on our preliminary phenotypic characterization of stonin 2 knockout (KO) mice. In contrast to its invertebrate orthologs Unc41 and stoned B, we find that stonin 2 KO mice are viable and fertile. However, analysis of the brain gross morphology reveals abnormal dilatation of the lateral ventricle, a defect that progresses with aging. Together with the observed astrogliosis in the hippocampus and cerebral cortex of KO mice these data suggest that loss of stonin 2 is accompanied by progressive neurodegeneration. Consistent with these defects we find that expression of stonin 2 in the brain dramatically increases postnatally with highest protein levels within the stratum lucidum of the hippocampal CA3 region. Furthermore, immunohistochemical analysis of the distribution of various endocytic and synaptic proteins within this area indicates that deletion of stonin 2 causes corresponding selective and significant loss of its direct binding partners synaptotagmin 1 and AP-2, while other presynaptic proteins such as synapsin 1 and synaptobrevin 2 remain unaltered. Based on these preliminary results we speculate that stonin 2 is required for normal brain morphology and regulates presynaptic function via maintaining a subset of SV and/ or endocytic proteins. Current studies are aimed at unravelling the underlying molecular mechanisms as well as the physiological and behavioral defects originating from these changes in stonin 2 KO mice.

32 SPINAL CORD INJURY INDUCES DIFFERENTIAL EXPRESSION OF THE PRO-FIBROTIC SEMAPHORIN 7A IN THE DEVELOPING AND MATURE GLIAL SCAR

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Semaphorin 7a (Sema7A) is involved in the formation of the central nervous system (CNS) during development by operating axon guidance and neuronal migration. We investigated the expression of the TGFb inducible Sema7A following spinal cord injury. After SCI, Sema7A+ cells accumulated specifically in lesion areas resulting in significantly enhanced Sema7A expression at the injury site ($p<0.0001$). During the first days lesional Sema7A expression was confined to neurons, ballooned neurite fibers/retraction bulbs and endothelial cells. With day 7 we observed Sema7A expression by components of the glial scar, such as reactive astrocytes and pronounced extracellular Sema7A deposition. In the direct peri-lesional rim Sema7A$^+$ astrocytes co-expressed the activation associated intermediate filament vimentin. In the injured spinal cord, numbers of Sema7A$^+$ cells reached maximum levels at day 14. The restricted accumulation of Sema7A$^+$ reactive astrocytes and Sema7A deposition in fibronectin$^+$ ECM territories suggests a participation of the fibrostimulatory Sema7A in the developing and maturating scar following SCI. In addition, Sema7A appears to be marker for astrocyte activation.

33 FREE RADICAL FORMATION AND MITOCHONDRIAL DAMAGE IN EPILEPSY – A REPERFUSION INJURY

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Several lines of evidence indicate that reactive oxygen species (ROS) formation is enhanced during epileptic activity leading to mitochondrial dysfunction, energy failure and neuronal cell death. Nevertheless, the sources and targets of ROS have not been identified yet. Here we studied kinetics and spatial pattern of ROS formation in an *in vitro* model of epilepsy by using electrophysiology, oxygen electrode recordings, microfluorimetry and confocal microscopy. Seizure-like events (SLEs) were associated with biphasic transients of NAD(P)H fluorescence, indicating initial oxidation (dip) followed by a lasting reduction (overshoot) of NAD(P)H. Tissue pO_2 decreased by ~130 mmHg during SLEs, but it remained clearly hyperoxic. NAD(P)H dip and overshoot were significantly faster than the peak and recovery of pO_2, respectively. Decreasing electron transport chain activity in the presence of high O_2 and increased NAD(P)H/NAD(P)$^+$ ratio was associated with an increase in ROS formation, as revealed by the oxidation of mitochondrialy targeted hydroethidine (MitoSox). Co-localisation of MitoSox with mitochondrial as well as with neuronal and astrocytic markers indicated ROS formation in neuronal mitochondria. Mitochondria showed considerable heterogeneity in shape, motility and MitoSox fluorescence. Mitochondria with high levels of ROS were less motile and occasionally underwent thread to grain transition. Remarkably, massive ROS formation was observed in mitochondria of capillary pericytes, leading to contraction of capillaries at late stages of the experimental status epilepticus. Thus we concluded that ROS formation occurs in neurons when electron transport chain activity decreases in the presence of high levels of reducing equivalents and O_2. Such conditions may occur *in vivo* during seizure associated increases in blood flow, whereas ROS dependent capillary constriction might be responsible for disturbances of neurovascular coupling during status epilepticus.

34 EXPRESSION PATTERN OF CDK5RAP2 IN MURINE BRAIN DEVELOPMENT

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Cyclin dependent kinase 5 regulatory subunit-associated protein 2 (CDK5RAP2; synonym C48, CEP215, MCPH3) is a centrosomal protein associated with centrosomal function, accumulation of pericentriolar material, spindle checkpoint function and microtubule dynamics in tumor cell lines. Homozygous mutations in the *CDK5RAP2* gene have been recently identified as a cause for primary autosomal recessive microcephaly (MCPH). MCPH is characterized by an isolated reduction of the brain volume, particularly of the cerebral cortex, with grossly preserved brain morphology. Only individual patients show neuronal heterotopias as a sign of a migration defect. Still, the exact function of CDK5RAP2 in physiological brain development and the pathomechanisms how its dysregulation induce the pathologic phenotype of MCPH are not known. CDK5RAP2 regulates CDK5 via binding to the CDK5 regulatory subunit 1 (CDK5R1), but the precise interactions are not revealed yet. Here, we describe the temporal and spatial expression pattern of Cdk5rap2 in murine brain development. Cdk5rap2 is highly expressed and synthesized during early stages of development and quickly down-regulated after birth. Immunopositivity is high in the ventricular and subventricular zone during early embryonal stages and can postnatally be detected in all cortical layers. This expression pattern underlines the function of Cdk5rap2 in cell proliferation and future studies will address its subcellular localization. Preliminary results show a slight but significant reduction of *Cdk5* mRNA expression in murine neuroblastoma (N2A) cells transfected with *Cdk5rap2* shRNA plasmids, indicating a regulatory feedback mechanism between these players. Further studies will focus on the effects of Cdk5rap2 overexpression and silencing on specific developmental processes of the CNS that contribute to brain growth.

35 PIGMENT EPITHELIUM DERIVED FACTOR AS AN IMMUNOLOGICAL MODULATOR

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PEDF, pigment epithelium derived factor, has been described as a multifunctional protein with various neurobiological properties such as neuroprotective and neurotrophic. It also shows very potent anti-angiogenic, anti-tumour and anti-permeability effects. Recent lines of evidence suggest that PEDF may additionally possess immunomodulatory activities. We therefore intend to explore this aspect by analyzing the effects of PEDF on migration, homing and trafficking of leukocytes with a focus on CNS injury. Our approach comprises the Boyden chamber assay, a static *in vitro* transmigration model. This mimics the transmigration of immune cells across an endothelial cell layer towards a chemoattractant; here the CSF of patients with multiple sclerosis, meningitis, pseudo tumour cerebri or epilepsy. Additionally the PEDF concentration in CSF and serum is analyzed by ELISA. To understand the underlying mechanisms of PEDF's action, expression levels of adhesion molecules (E-selectin, ICAM-1, VCAM-1) are determined on endothelial cells and on molecules involved in trafficking of OT-2 cells such as adhesion molecules (LFA-1, VLA-4, ICAM-1) and chemokine receptors (CCR5, CCR7, CXCR3, CXCR4). Also the activation

status is monitored by CD25 and CD62L analysis. All above mentioned expression studies are performed by RT-PCR and FACS. Our results indicate that PEDF reduces activation of lymphocytes and increases the expression of homing receptors. Furthermore we found a correlation between the number of transmigrating cells and PEDF concentration in the transmigration assay. We therefore suggest that PEDF may indeed function as an immunomodulator by inhibiting leukocyte activation and promoting chemokine homing receptor expression.

Poster Presentations - Session II
Friday, June 11, 2010, 14.30 - 16.30

36 MICROGLIA INDUCED REGULATORY T CELLS (TREGS) SUPPRESS EXPERIMENTAL ALLERGIC ENCEPHALOMYELITIS (EAE)

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Microglial cells are the major immune competent cells of the brain. Activated microglia are able to process and present antigen to initiate innate and adaptive immune responses. Their activation is observed in various CNS affecting diseases and injury models including brain ischemia, enthorinal cortex lesion (ECL), or EAE. This study was designed to elucidate the complex cross-talk between microglia and brain infiltrating immune cells, specifically the direct microglia–T cell interaction. Therefore, primary microglial cells were treated with different doses of IFNgamma and neuronal antigen (MOG_{35-55}) and then co-cultured with naïve CD4+ T cells derived from T cell receptor transgenic mice specific for MOG. Here we demonstrate for the first time, that depending on their activation status, microglia induce either a effector T cells response, when activated with a high-dose [100U/ml IFNgamma–10μg/ml MOG], or FoxP3+ Tregs, when challenged with a low-dose [10U/ml IFNgamma–1μg/ml MOG]. Microglial T cell stimulatory capacities proved to be strictly MHC class II dependent and antigen specific. Interestingly, the co-stimulatory molecules CD40 and CD86 were expressed at intermediate levels on low-dose activated microglia, whereas high-dose leads to high expression levels. We also found low-dose activated microglia to produce significant more IL10 compared to high-dose stimulation, pointing out a tolerogenic microglial phenotype. Microglia-induced Tregs proved to be functionally active *in vitro*, by inhibiting antigen-specific proliferation of effector T cells, and *in vivo*, by attenuating EAE disease course and onset of disease after Tregs were adoptively transferred. In sum, our data demonstrate that microglia display activation-dependent phenotypes and therefore may be involved in maintaining the balance between inflammation and regulation.

37 BLOOD BRAIN BARRIER BREAKDOWN: ABNORMAL PLASTIC CHANGES AS A PRECURSOR FOR EPILEPTOGENESIS

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Common neurological diseases with an ischemic component, such as stroke and head injury, can lead to epilepsy in humans. Interestingly in recent studies these diseases were shown to be correlated to a breakdown of the blood-brain-barrier (BBB). However it is still unknown which mechanisms are behind the breakdown of the BBB in the epileptic tissue, and whether per se the BBB breakdown plays a role in epileptogenesis. In previous studies from our group it was shown that in a model of BBB breakdown with albumin, the most abundant protein in blood which normally doesn't cross the BBB, a dysfunction of astrocytes in the neocortex of the rat was observed, which leads to an altered homeostatic microenvironment for neuronal transmission, namely accumulation of K+ and glutamate, which in turn is strongly dependent on the neuronal firing frequency. These previous results encourage us to investigate whether these altered neuronal microenvironment transmission after the BBB breakdown could lead to abnormal neuronal plasticity in different neuronal frequencies. Therefore we investigated here the frequency-dependent changes in synaptic plasticity in the hippocampus Schaffer-collateral to pyramidal cells synapses using in-vitro albumin exposure (0.2mM) for 1 hour in acute slices of rat's hippocampus. Our preliminary results suggest that in albumin slices after the application of low (20Hz) frequency bursts-stimuli, there is an enhanced long-term-potentiation (LTP).

Supported by a grant of the Deutsche Forschungsgemeinschaft to Sonderforschungsbereich TR3

38 DYNAMICAL SWITCHING BETWEEN NETWORK STATES IN HIPPOCAMPAL AREA CA3

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It have been shown that the cell-interneuron network in area CA3 can exhibit different network states (theta and gamma regimes) and can switch between them. It was shown earlier that this switching is controlled by the synaptic conductance between interneurons (basket- and O-LM cells) and pyramidal cells. The minimal network scheme, describing connections between different types of cells and its detailed model have been studied in [1,2]. Using this model we have studied how the period and the phase shift between oscillating cells depend on strength of synaptic connections. In the space extended system we have investigated gamma and theta waves and the switching between them.

Supported by BCCN Proejkt A3

39 PROTEOMIC ANALYSIS OF A NEUROPROTECTIVE MITOCHONDRIAL MULTIPROTEIN COMPLEX

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Mitochondrial multiprotein complexes are involved in the regulation of programmed cell death. In particular, the voltage dependent anion channel (VDAC) of the outer mitochondrial membrane serves as an anchor of numerous proteins regulating apoptosis. We have previously identified a protein complex with antiapoptotoc and neuroprotective properties centered around the glycolytic enzyme Hexokinase II, which is also known to bind to VDAC. Apart from its importance for glucose metabolism, mitochondrial Hexokinase II is able to regulate apoptosis. Mitochondrial localization of a putative Hexokinase II-centered multiprotein complex is essential for neuroprotection, thereby integrating two fundamental cellular pathways: apoptosis and metabolism. We identified core components of this antiapoptotic complex by a genetic screening approach in yeast, thereby missing interactions based on posttranslational modifications in mammalian cells. We are therefore applying a proteomics approach to detect missing interactors and characterize the exact composition of the Hexokinase II associated complex. Mitochondria from rat brain tissue and primary neuronal cell cultures are isolated under native conditions. In order to preserve the conformation of the membrane-associated proteins within the complex, we are purifying mitochondrial protein complexes by blue-native electrophoresis. Experimental strategies and preliminary results leading to structural and functional insight into the molecular composition of the antiapoptotic Hexokinase II multiprotein complex will be presented.

The research leading to these results has received funding from the European Union's Seventh Framework Programme (FP7/2007-2013) under grant agreements n° 201024 and n° 202213 (European Stroke Network).

40 MANIPULATING ALZHEIMER'S DISEASE BY TRANSGENIC RESTRICTION OF ANTI-AMYLOID-ÂETA ANTIBODIES TO THE PERIPHERY

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To address whether anti-Aâ antibodies during Aâ immunotherapy exert their action (i.e. brain Aâ plaque clearance) in the periphery or within the CNS, we transgenetically restricted anti-Ab antibody expression to the periphery, similar as described earlier (Heppner et al., 2001). The first transgenic line, AB9μ, expresses the Aâ-specific mAB9 heavy chain VDJ region (Das et al., 2003) under the control of the endogenous IgM heavy chain promoter and enhancer, resulting in the production of a soluble form of Aâ-specific IgM antibodies. Due to the pentameric form, anti-Aâ IgM antibodies derived in AB9μ mice are supposed not to efficiently cross the BBB. By deleting the gene segment controlling the secretion of Aâ-specific B cells, a second transgenic line AB9μ-delS was generated, which is capable of expressing a membrane-bound form of Aâ-specific antibodies without releasing soluble Aâ-specific antibodies. Transgenic founders of both mouse lines were established by pronuclear microinjection, a detailed assessment including the analysis of Aâ-specific titers is presently ongoing. Mice expressing functional anti-Aâ IgM antibodies will be crossed to APP/PS1 Alzheimer mice (Radde R et al., 2006) in order to test whether anti-Aâ antibodies outside the CNS are sufficient to lower amyloid plaque burden by acting as a "peripheral sink" (DeMattos et al. 2002).

Funded by grants DFG Exc 25, DFG SFB TRR43 and NIH NINDS R01 to FLH

41 MYELINATION IN THE MOUSE CEREBELLAR WHITE MATTER DEPENDS ON OLIGODENDRO-CYTE TO ASTROCYTE COUP-LING MEDIATED BY CONNE-XIN47 AND CONNE-XIN30

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We recently demonstrated that oligodendrocytes form gap junctional channels among each other and with astrocytes in the corpus callosum *in situ*. At oligodendrocyte-to-astrocyte gap junctions oligodendrocytic connexins (Cx) Cx47 and Cx32 colocalize with astrocytic Cx43 and Cx30. We now studied oligodendrocyte-to-astrocyte coupling in acute cerebellar slices of Cx47/Cx30-double-deficient (Cx47/Cx30 dKO) mice. By whole cell patch clamp single oligodendrocytes were dialysed with the gap junction-permeable tracer biocytin. In wildtype, biocytin spread to neighbouring cells in 41% of the injections, in Cx47/30 dKO we found coupling in 74% of injections. The average number of coupled cells per network was identical (29 ± 6 cells) in wildtype and Cx47/30 dKO. In wildtype, 93 ± 2% of the coupled cells expressed the oligodendrocytic marker CNPase while 7 ± 2% were positive for the astrocytic marker GFAP. In Cx47/30 dKO all biocytin-positive cells were oligodendrocytes expressing eGFP under control of the Cx47 promoter. Thus, ablation of Cx47 and Cx30 abolished oligodendrocytic to astrocytic coupling. During P40-80, 36% of the Cx47/Cx30-deficient animals die exhibiting profound abnormalities in cerebellar white matter and corpus callosum, characterized by thin myelin sheaths, vacuolization and massive microglial activation. In cerebellar white matter MBP and CNPase expression were drastically reduced, while in corpus callosum mainly CNPase expression was affected. We conclude that normal myelin morphology and function depends on oligodendrocyte to astrocyte coupling and that expression of Cx32 and Cx43 cannot compensate for loss of Cx47 and Cx30.

42 INHIBITION OF OPIOID PEP-TIDE DEGRADATION FOR AN-ALGESIA IN PERIPHERAL INFLAMED TISSUE

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During the course of inflammation, circulating immune cells are recruited to the damaged tissue where they release opioid peptides such as â-endorphin, enkephalins and dynorphin. Secreted opioids bind to their receptors located on the peripheral terminals of sensory neurons resulting in decreased neuronal excitability and consequently in reduced pain sensation (Stein et al., Nat Med, 2003). Two membrane metallopeptidases, neutral endopeptidase (NEP) and aminopeptidase N (APN), have been shown to be involved in the degradation of opioid peptides, mainly the enkephalins. Based on these findings, our first goal is to verify if immune cells containing opioid peptides also co-express their degrading enzymes. Secondly, we would like to examine whether blocking NEP and APN results in increased opioid peptide concentrations directly in inflamed painful tissue. In a rat model of unilateral hindpaw inflammation, using immunofluorescence, both NEP and APN were detected on opioid peptide-containing immune cells. In preliminary *in vivo* microdialysis experiments, increased extracellular enkephalin concentrations were measured in the inflamed tissue following the application of either corticotrophin releasing factor or of peptidase inhibitors. Inhibiting the enzymatic degradation of endogenous opioids offers a promising strategy for the pain control without adverse centrally-mediated side effects.

Supported by a grant of the Deutsche Forschungs-gemeinschaft

43 EGCG AND GLATIRAMER ACETATE EXERT SYNERGISTIC NEUROPROTECTION IN EXPERIMENTAL AUTOIMMUNE ENCEPHALOMYELITIS

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Multiple sclerosis (MS) is a common inflammatory disease of the central nervous system. There is accumulating evidence from studies of MS and the animal model experimental autoimmune encephalomyelitis (EAE), that neuronal pathology plays a critical role early in disease, in addition to inflammatory processes. Furthermore, neuronal damage is the principle cause of disability in later stages of MS, when inflammatory processes play a lesser role. Despite this, current therapies for MS are directed toward immune processes. There is therefore a need to develop new therapeutic strategies that focus on both neuroprotection and immunomodulation. We previously showed that epigallocatechin-3-gallate (EGCG), a constituent of green tea, inhibited clinical severity of EAE. In the present study we evaluated the effects of combined

treatment with EGCG and glatiramer acetate (GA), a standard immunomodulatory MS therapeutic. A synergistic effect of EGCG and GA was seen in *in vitro* cell death assays; HT22 hippocampal cells showed significantly less glutamate-induced apoptosis when treated with EGCG and GA, compared to the single treatments. Synergistic effects of EGCG and GA were also seen in a hippocampal slice culture axon outgrowth assay: treatment with EGCG and GA showed significantly increased axon number and thickness, compared to single treatments. When administered *in vivo*, EGCG and GA significantly reduced the clinical severity of EAE, and again this effect was greater than with either compound alone. These results strengthen the prospects of EGCG as an adjunct therapy for neuroinflammation, and underscore the necessity of testing combined anti-dengenerative and anti-inflammatory therapies.
Supported by ECRC.

44 CELLULAR UPTAKE OF PIGMENT EPITHELIUM DERIVED FACTOR BY U87 GLIOBLASTOMA CELLS

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Pigment Epithelium derived Factor (PEDF) is a multifunctional factor with antiangiogenic, neurotrophic and neuroprotective activities. There is, however, very little knowledge about the signal transduction mechanisms responsible for these multiple effects, in particular since it has proven hard to identify PEDF receptor/s and only binding proteins have been reported. In our project we test the hypothesis that instead of starting a signal transduction cascade by binding to a membrane receptor, PEDF is endocytosed and transported to the cytosol, where it acts directly inside the cell. Cells of the U87 human glioblastoma cell line, which have been reported to react to PEDF stimulation by undergoing cell cycle arrest and apoptosis, were incubated with PEDF for different time periods. Cells were lysed and PEDF content of the lysate was detected by ELISA. Under the same experimental set up, we will use specific inhibitors to stop the endocytosis process (Brefeldin, Bafilomycin). Double immunocytochemistry stainings will be performed to detect the intracellular localization of internalized PEDF. Our preliminary results show that compared to controls where no PEDF has been given to the cells, PEDF intracellular content increases, starting at incubation times of mere minutes. Until now our results indicate that PEDF might be taken up by U87 suggesting direct action inside the cell instead of at a membrane bound receptor.

45 EFFECT OF DECANOIC ACID ON CELLULAR INTERNALI-ZATION OF CLAUDIN-5

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The blood-brain barrier (BBB) is formed by a monolayer of brain capillary endothelial cells, sealed by tight junctions (TJ). Of the major components of TJ, claudin-5 has been shown to be involved in size-selective opening of the BBB, affecting barrier integrity for small molecules (<800 Da). Sodium decanoic acid, also known as caprate, opens TJs in the epithelial cell lining, decreasing transepithelial electrical resistance and increasing paracellular permeability. However, little is known about the intracellular fate of claudins upon treatment of the cells with caprate. Therefore, we investigate the possible influence of caprate on claudin internalization in stably claudin-5-YFP (yellow fluorescent protein) transfected HEK (human embryonic kidney) 293 cells. In order to study the localization of claudin-5, a membrane marker, FM4-64FX, which is quickly endocytosed and thus suitable for studying vesiculation, is applied. By this means, co-endocytosis of labelled claudin and fluorescent dye is to be monitored using confocal fluorescence microscopy. Preliminary investigations showed that untreated control as well as caprate treated cells exhibit 0 to 10 YFP-containing particles in the cytoplasm, whose size and number did not change significantly over time. However, a sharp time-dependent increase in internalization of vesicles labelled with the membrane dye was monitored in caprate-treated cells as compared to the control. Some – but not all - of the formed vesicles were shown to contain YFP in intensities above the background cytosolic level. These first observations suggest the possibility of elevated endocytic events and internalization of TJ proteins upon caprate treatment. Further investigations are proposed aiming at confirming the preliminary observations and of identifying the nature of the internalized structures. To that end, different endocytosis pathways will be analyzed by specific knock-down and inhibition, co-localization studies with endosomal markers and by applying pathway-specific tracers.

46 EXTRACELLULAR ION CONCEN-TRATION CHANGES IN CORTI-CAL SPREADING ISCHEMIA

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Cortical spreading depolarization (CSD) waves are associated with massive pertubations in ion distribution, but do not lead to neuronal damage in the normal brain. In the diseased brain, CSD waves can be associated with cortical spreading ischemia (CSI). In global and focal ischemia loss of Ca^{2+}

homeostatic control and cellular Ca^{2+} overload promote cell death. The question if such detrimental calcium changes occur in CSI has not been adressed. Here we investigated the disturbances of ion homeostasis in relation to CSI. Specifically, the duration of extracellular concentration changes of K^+, Na^+, Cl^- and Ca^{2+}, were analyzed and compared with the duration of the accompanying direct current (DC) potential shifts, pH and CBF changes. In anesthetized, wistar rats (n=32), equipped with an open, cranial window the intracortical DC potential and extracellular changes in K^+, Na^+, Ca^{2+}, Cl^- and pH were measured with microelectrodes and CBF was recorded by LDF. The cortex was superfused with artificial cerebrospinal fluid in a composition known to induce CSI. The duration until normalization of the individual ion concentrations was measured and compared to the duration of the corresponding DC potential shift and CBF change. The mean duration of CSD induced CBF hypoperfusion was 17.2 (+/- 13.4) min. (+/- SD) and correlated significantlly with the duration of the DC potential shift (23.7 +/- 14.6 min). The duration of the CSD/CSI induced decrease in extracellular Na^+ and Cl^- and the increase in K^+ showed no difference to the duration of the DC change. In contrast, the duration of the extracellular Ca^{2+} decrease was significantly longer. Our findings suggest that intracellular calcium accumulation might contribute to tissue damage in CSI.

47 FULLY AUTOMATIC DELINEA-TION OF HYPOPERFUSED TISSUE IN PERFUSION MRI COMPARED TO A SEMIAUTO-MATED APPROACH RESULTS IN CONSIDERABLE DISCREPANCIES IN PERFUSION DEFICIT VOLUMES

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Using MRI several methods are available to assess the hypoperfused areas in patients with acute ischemic stroke (AIS). Previously, studies dealing with volumes of hypoperfused tissue used either a manual approach to lesion delineation or an automated approach with predefined thresholds. We compared volumes obtained through a partially manual method, based on combining thresholds with human judgement, with those calculated by a fully automated method. We retrospectively included 145 AIS patients who had perfusion MRI performed within 24 hours of AIS. Using Stroketool we calculated perfusion maps of 3 parameters (MTT, CBF and Tmax) with three different thresholds for each parameter. The 9 resulting maps were then post-processed using two different procedures. In the manual procedure, a human rater drew a region of interest around the areas where hypoperfusion was credible and measured the resulting volume. In the automated procedure, areas of CSF were excluded from the thresholded maps in a fully automatic step and the remaining volumes were calculated. Volumes calculated by the automatic method were in 98,6% of cases larger than those derived with human input and the mean difference in the volumes between the two methods ranged from 24ml to 205ml.The level of agreement between these two methods was assessed using Bland-Altman plots. We could show considerable discrepancies between the two methods for all of the 9 maps and the degree of agreement was not acceptable. Of all the calculated maps the Tmax map showed the lowest level of discrepancies. We conclude that automated protocols still require substantial refinement in order to produce credible results.

48 SIP1 CONTROLS NEURITE OUTGROWTH IN CORTICAL NEURONS AND ORCHESTRATES CORTICAL CONNECTIVITY

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Appropriate neuronal connectivity, axonal growth and guidance is one of the most tightly and robustly regulated process during neural development. We previously showed that Sip1 is a transcriptional repressor expressed primarily in cortical postmitotic neurons. In this study, we show that Sip1 deletion within neocortical neurons leads to widespread effects on Neocortical connectivity. Sip1 mutants lack neocortical commissural connections such as the Corpus Callosum and Anterior Commissure, while the hippocampal commissure is preserved. While corticothalamic and thalamocortical connections are largely spared in these animals, Cortico-subcerebral projections are largely missing. While the number of fibers passing through the cerebral peduncle was significant in these animals, there was hardly any contribution to the cerebral peduncle from the neocortex. However, the few neurons that project subcerebrally are correctly specified and their lamination is preserved. We noticed an ectopic projection of upper layer neurons into the internal capsule, however these neurons do not project either to the thalamus or subcerebral structures. Our data shows that Sip1 controls neurite outgrowth cell-autonomously. Sip1 deletion leads to retardation in neurite outgrowth and these neurons fail to develop long axons. We hypothesize that Sip1 deletion leads

to a neurite outgrowth problem, which is pronounced within the population of subcerebrally projecting neurons. We investigated the role of early B-cell factor-1 or Ebf1 in neurite outgrowth, since the expression of this transcriptional factor is increased in Sip1 deleted cortices. Preliminary data suggests that Ebf1 could be preventing neurite outgrowth in Sip1 mutants.

49 CORRELATION OF RETINAL NERVE FIBER LAYER THICKNESS IN OPTICAL COHERENCE TOMOGRAPHY WITH VISUAL CORTEX MR SPECTROSCOPY AND BRAIN ATROPHY IN MUL-TIPLE SCLEROSIS

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Retinal nerve fiber layer thickness (RNFLT) measured by optical coherence tomography (OCT) is a novel parameter in MS diagnostics. It promises a simple and valuable tool for in vivo assessment of neurodegeneration in MS. Recently, a correlation between brain atrophy and RNFLT could be shown. However, a potential mutual association of RNFLT with the visual nervous system as well as with whole brain neurodegeneration still needs to be better understood. In a cohort of relapsing-remitting MS patients (n=78) RNFLT reduction was assessed by time domain OCT. Brain Parenchymal Fraction (BPF) was calculated from routine MRI. Brain tissue metabolites were measured by 3T MR spectroscopy (MRS) in two voxels in the frontoparietal normal appearing white matter (NAWM) and in a visual cortex (VC) voxel. All findings were analyzed using Pearson's Correlation and Generalized Estimating Equations (GEE). RNFLT correlated with N-acetylaspartate (NAA) concentration ($p=0.042$) and the NAA/creatine ratio (NAA/Cr; $p=0.011$) in the VC, but not in the NAWM voxels. BPF was correlated with RNFLT ($p=0.009$) and highly correlated with NAA ($p<0.001$, $p=0.003$) and NAA/Cr ($p=0.032$, $p=0.001$) in the NAWM in both hemispheres, but not with NAA or NAA/Cr in the VC. In a multivariate GEE, BPF and VC NAA/Cr in combination were good predictors for RFNLT reduction. We concluda, that RNFLT correlates well with NAA measured by MRS in VC and with BPF, each method providing a partial view on different pathophysiological aspects of MS. Interestingly, our findings point to an interplay between neurodegeneration of the anterior visual pathways and the VC and, moreover, may indicate a focal affection of a particular functional system (in this case the visual system) exceeding diffuse global neurodegeneration.

50 CENTRAL GLUTAMATERGIC TRANSMISSION IS CONTROLLED BY LYSOPHOSPHATIDIC ACID

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Lysophosphatidic acid (LPA) is a mediator that produces diverse cellular and biochemical responses 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, with LPA-2 receptors exhibiting the highest expression. Therefore, we focused on the LPA-2 receptor subcellular localization in hippocampal primary neurons. We found receptor expression in the cell body, dendrites and axon structures. Interestingly, it was colocalized with pre-synaptic markers and was present in glutamatergic, but not in GABAergic, neurons. In functional analyses we tested the effects LPA on primary neurons. Changes in the extracellular LPA concentration mediated inositol (1,4,5) trisphosphate (IP_3)-induced Ca^{2+} release (IICR), which in turn activated P/Q-type calcium channels. Our results show that this signaling modulates spontaneous vesicle release probability. We showed that LPA seems to inhibit the dynamic of synaptic vesicle recycling, which finally results in a decrease of mEPSCs frequencies, despite the initial activation of the molecular pathway for neurotransmitter release. Fura-Red imaging of primary differentiated hippocampal mouse neurons demonstrated that LPA stimulated Ca^{2+} increase in presynaptic terminals, visualized by Synapto-pHluorins.In conclusion, our experimental results show that LPA plays a novel role in the regulation of glutamatergic transmission and demonstrate the important and manifold effect of this bioactive phospholipid.

51 HIGH-FREQUENCY OSCILLA-TIONS IN THE HIPPOCAMPUS FOLLOWING ABLATION OF INHIBITION ONTO PARVAL-BUMIN-POSITIVE CELLS

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Network „ripple" oscillations (140-200 Hz) in the hippocampal CA1 area have been implicated in memory processing. Yet mechanisms of their generation are not well understood. Here we studied ripple oscillations following genetic ablation of synaptic inhibition onto parvalbumin-positive (PV) cells. In contrast to controls, PV-$Ä\bar{a}_2$ mice displayed in vivo virtually no oscillatory events with leading frequencies in the 140-200 Hz band. Local field potential (LFP) and unitary activity during ripple-like events in PV-$Ä\bar{a}_2$ mice were organized at fast gamma frequencies.

Ripple oscillations in both genotypes were accompanied by LFP sharp waves in the CA1 stratum radiatum and associated patterns of population synchrony in the CA3 area. These results suggest that the generation of ripple oscillations in the intact CA1 area require mutual inhibition between PV cells.

52 SILENCING NEURONAL ACTI-VITY WITH A DESIGNER RECEP-TOR ACTIVATED BY A DESIGNER DRUG

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Cell specific, rapid and reversible silencing of neuronal communication *in vivo* presents a long-standing desire of system neuroscientists. Despite numerous attempts to tackle this challenge, a satisfying technique that fulfils all needs is still lacking. So far, the methods presented rely on expression of toxins, which is neither rapid nor reversible, or of pharmacological interventions that depend on endogenous transmitter systems or ligands that are not blood brain barrier permeable. We investigated the applicability of a novel designer receptor activated by a designer drug (DREADD) for the above mentioned criteria. In primary hippocampal cell cultures the DREADD was expressed with a lentivirus. Patch clamp experiments on the infected neurons revealed that nanomolar concentrations of a blood brain barrier permeable small molecule activates the receptor and efficiently shuts down neuronal communication. We now develop of a mouse model expressing the DREADD under control of a strong CAG promoter in the Rosa26 locus, using a FELX cassette (flip-excision) to provide cell type specific expression by Cre-driver lines. Additionally, a lentiviral system with a floxed GFP-stop in front of the DREADD is established that offers the advantage of site specific expression of the DREADD.

53 STABILITY OF DIFFERENT BIO-MARKER PROTEINS IN LONG-TERM STORED HUMAN CEREBR-OSPINAL FLUID

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The quantitative analysis of biomarkers, like total-Tau, Aß 1-40 and Aß 1-42 in human cerebrospinal fluid (CSF), is a crucial step in analyzing the neurobiological basis of chronic neurodegeneration (i.e. Alzheimers disease) and disease progression. Large biobanks containing thousands of specimens from clinically well characterized patients have been built up within the last years. Here we performed repeated quantitative biomarker analysis in CSF samples that had been frozen for several years to elucidate the durability of the proteins. We re-evaluated the total-Tau and Aß-values in aliquots of 16 CSF samples of different age (0-7 storage years) using two different methods; classical ELISAs (IBL and Innogenetics) and the Mesoscale system. For 41 CSF aliquots, the ELISAs were used for the initial quantitative analysis of Aß species, then, 4-5 years after collection, aliquots of the samples were determined using the Mesoscale System. We found that in CSF samples that have been for stored at -80°C for up to 7 years, the biomarkers Aß 1-40 and Aß 1-42 can be determined even when the protein in those samples is denatured. The quantification of Aß species was reproducible using the different kits and methods. For total-Tau, the different methods gave reproducible results in samples up to 3 years of age. In older samples (up to 7 years), only the ELISA (Innogenetics) yielded reliable results. The quantitative analysis of the concentration of the Abeta-species Aß 1-40 and Aß 1-42 in CSF using different methods is reliable, even in samples that have been stored for years. For the analysis of total-Tau in CSF some limitations concerning the method emerge in samples older than 3 years. Therefore, the determination of these biomarkers in the CSF stored in large biomaterial banks assembled over many years is feasible.

54 A YEAST TWO HYBRID SCREEN FOR INTERACTION PARTNERS OF TRPV1, TRPM8 AND TRPA1

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Thermosensitive transient receptor potential (TRP) channels are a family of six-transmembrane cationic channels expressed in sensory neurons and activated by noxious hot and cold temperatures. They are also activated by pungent compounds like capsaicin (TRPV1) and menthol (TRPM8) that mimic hot and cool sensations, and by chemical irritants found in car exhaust and tear gas (TRPA1). Furthermore, in addition to their roles in temperature and chemical sensation, TRPV1 and TRPA1 are sensitized or upregulated in response to inflammation and result in hyperalgesia (increased sensitivity to pain). While various activators of the channels and their roles in sensory perception are increasingly understood, less is known about the channels' local environment at the membrane, including proteins that associate with or modulate their function. We therefore expressed the cytosolic N-termini of rat TRP channels in yeast and screened a cDNA library generated from rat

dorsal root and trigeminal ganglia in a yeast two hybrid system to identify interacting proteins. These 430-720 residue-long tails contain ankyrin-binding domains and, unlike the full channel, can be expressed in yeast. Our goal is to identify and validate potential interaction partners using other methods, and then characterize their role in the context of normal function and inflammation.

55 MAGNETIC RESONANCE ELASTOGRAPHY DETECTS REDUCED VISCOELASTICITY IN AN ANIMAL MODEL OF CNS DEMYELINATION

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Magnetic resonance elastography (MRE) is a novel imaging technique non-invasively quantifying viscoelastic tissue properties and structural integrity *in vivo*. In our experiment, we studied sixty C57/b6-mice. Feeding the neurotoxicant cuprizone (CPZ) induced transient demyelination of the central nervous system (CNS), mimicking the myelin damage and repair during neuroinflammation, e.g. multiple sclerosis. CPZ-enriched diet was delivered during 6 weeks, followed by another 6 weeks of regular feeding. Applying a ultra high field rodent MRI (Bruker Pharmascan 7 Tesla), we performed full 3D MRE with an isotropic image resolution of 300μm. Longitudinal mechanical waves at 1000Hz were transmitted into the mouse brain. High-resolution T2-weighted anatomical scans were additionally acquired with identical slice positioning. The complex-valued shear modulus $G^* = Gd + iGl$ was calculated in regions of interest on reconstructed maps. Anatomical details depicted on the resulting maps for elasticity and viscosity, such as the corpus callosum, the olfactory cortex and other CNS structures, correlated closely with those on high resolution morphological images, differentiating stiff and viscous brain regions. In the longitudinal experiment, a reduction of viscoelasticity started 3 weeks after treatment onset. Demyelination became visible on T2-weighted MRI with a delay of at least 3 weeks. When cuprizone food was withdrawn, viscoelasticity levels and T2 signal alterations recovered. In conclusion, we could demonstrated that high-resolution MRE at 7T of the murine brain can detect CNS demyelination in cuprizone treated C57/black6 mice. Viscoelasticity maps matched closely with anatomical details. CPZ-mice developed significant decreases in viscoelasticity and recovered after the treatment was withdrawn.

56 PKC EPSILON IN PROTEIN TRANSLATION

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The epsilon isoform of protein kinase C plays an important role in models of pain sensitization. Recently, we described a signaling pathway toward activation of PKCå. Nevertheless, downstream effectors of PKCå are mostly elusive. On protein arrays we now identified ribosomal proteins and modulators of protein translation as novel substrates of PKCå. Therefore we tested for the role of PKCå in one process of translational modulation, namely stress granule formation. In F-11 cells – a cell line derived from rat primary sensory neurons and mouse glioblastoma cells – we could show colocalization between stress granules and PKCå granules upon arsenite and heat treatment via immunofluorescence experiments. We further show that inhibition of the epsilon isoform of protein kinase C leads to a reduction of stress granule forming cells. Additionally we started to investigate effects of PKCå overexpression and knockdown. Our results indicate the involvement of PKCå in stress granule formation and thus in modulation of protein translation in F-11 cells. First results indicate this to be the case also for primary sensory neurons (DRG neurons). To what extend PKCå-dependent stress granule formation is involved in pain sensitization will be tested in future in behavioral experiments.

Supported by Deutsche Forschungsgemeinschaft

57 TRANSIENTLY DECREASED EXTRACELLULAR ATP CONCENTRATION DURING THE ONSET OF HIPPOCAMPAL GAMMA NETWORK OSCILLATIONS

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ATP is well known as energy supplier within cells and as extracellular signalling molecule released i.a. by neurons and glia acting at P2X and P2Y receptors. In the hippocampus, functional P2X and P2Y receptors have been found on astrocytes and interneurons. However, the extracellular level of ATP and its alteration in different network states is still unknown. Here, we investigated if the concentration of extracellular ATP changes during neuronal network activity. Therefore gamma oscillations (30-90 Hz) were induced in the CA3 region of acute hippocampal slices of the rat by using either acetylcholine (ACh) or kainic acid (KA). Changes in ATP concentration during oscillation induction were measured by using ATP-sensitive electrochemical biosensors. The average extracellular baseline level of ATP was determined to be approx. 0.5 μM. During the induction of ACh-oscillations, the concentration of

ATP declined by approx. the same value and recovered to baseline after the gamma oscillation reached its maximal power. This transient decline was only found in stratum pyramidale but not in stratum radiatum or oriens. In addition, the concentration of ATP did not change in any CA3 layer under KA-induced gamma oscillations. Nevertheless, the power of both types of gamma oscillations were concentration-dependently reducible by extracellularly applied ATP. In conclusion, our results suggest that ACh- and KA-induced gamma oscillations involve different neuronal pathways either or not influencing ATP release. During the initial induction phase of ACh-oscillations, the ATP concentration transiently decreases, permits the development of oscillations and subsequently recovers to the baseline level.

58 DEVELOPMENTAL AND CELL TYPE-SPECIFIC EXPRESSION OF THYROID HORMONE TRANS-PORTERS IN THE MOUSE BRAIN AND PRIMARY BRAIN CELLS

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Thyroid hormones are essential for development and function of the brain. Local concentrations of the receptor binding thyroid hormone, T3, are homeostatically adjusted by expression of deiodinases (Dio), enzymes able to activate T4 to T3 (Dio2) or inactivate T3 to T2 (Dio3). Thyroid hormones cannot diffuse through lipid bilayers, but depend on transmembrane transport proteins. One of these transport proteins is called monocarboxylate transporter 8 (MCT8). Mutations in *MCT8* lead to Allan-Herndon-Dudley syndrome, a severe mental retardation associated with abnormal thyroid hormone constellations. Mice deficient in *Mct8* exhibit the same endocrine changes as human patients, but do not suffer from severe neurological defects. We hypothesized that differential expression patterns of alternative thyroid hormone transporters in mice and men may underlie these discrepancies (1). To test this hypothesis further, we have investigated the expression of three different thyroid hormone transporters, i.e. Mct8, Lat1 and Lat2 in mouse brain during development and in primary cultures of neurons, astrocytes, and microglia. Expression of thyroid hormone transporters is dynamic during development. Neurons and astrocytes express Mct8, Lat1, and Lat2. Microglia express specifically Mct10 and Slco4a1 in addition to high levels of Lat2. Our conclusion that Mct8 and Lat2 both mediate thyroid hormone trafficking across the astrocytic plasma membrane was directly supported by functional assays. Thus, we have identified on a molecular level the thyroid hormone transporters in murine astrocytes.

59 MICROGLIAL CALCIUM SIGNALING *IN SITU*

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Microglial cells express a variety of receptors which are linked to calcium signalling via release from internal stores or by entry through the cytoplasmic membrane. We have previously studied microglial calcium signals *in vitro* using calcium sensitive dyes, but so far calcium signals in microglial cells *in situ* could not be analyzed, since no procedure to load the cells with calcium indicators has been found yet. To overcome this restriction we have created two retroviral constructs expressing GFP or the calcium sensitive construct GCaMP2. To test the construct *in vivo*, we made a stab wound in the cortex of adult mice to trigger microglial proliferation and injected the retroviruses two days later. First GFP-retrovirus was injected to confirm that the retroviral constructs can be expressed into proliferating microglial cells *in vivo*. GFP/BrdU-positive cells were found 3 and 6 days after the induction of the injury. At day 3, 6, 21 and 42 we identified GFP-positive cells as microglia by Iba-1 staining. At day 3, patch clamp recordings from GFP-positive cells revealed a current pattern of activated microglia characterized by inactivating inward currents and non-inactivating outward currents. At day 6 and day 21 only inward currents were recorded. 42 days after injury, the membrane conductance was very low, typical for ramified microglia cells. To measure microglial calcium signals we transduced the GCaMP2 retrovirus applying the same procedure as described above. We prepared acute brain slices and stained them with tomatolectin for identification of microglial cells. Ca^{2+} signals in response to ATP application were recorded from microglial cells which were located close to the lesion site at all time points tested (day 3, 6, 21 and 42). Microglial cells also exhibited Ca^{2+} responses to Substance P, endothelin, histamin and serotonin. We conclude that the retroviral vector approach in combination with a stab wound can be used to identify functional receptors linked to calcium signalling in microglia from brain tissue.

60 THE ROLE OF SATB2/CTIP2 AND FEZL IN CORTICAL CONNEC-TIVITY AND THE ELUCIDATION OF THEIR DOWNSTREAM PATH-WAYS

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Satb2 has been shown to control the post mitotic fate of cortical neurons that reside in the upper layers

(II-IV) of the developing neocortex, in part by downregulating the expression of Ctip2. Ctip2 is a transcription factor primarily expressed in layer V neurons, which are destined to form corticospinal connections (Britanova, 2008). In Satb2$^{-/-}$ the cortico-cortical connections fail to form and instead there is an ectopic induction of corticospinal connectivity. Ctip2$^{-/-}$ loose their normal corticospinal connections of layer V neurons which are instead misrouted into forming callosal projections (Arlotta, 2005). Fezl has been shown to control the fate of deep layer neurons, both corticospinal motor neurons and other subcerebral projection neurons, by inducing the expression of Ctip2 (Molyneaux, 2005). In Fezl$^{-/-}$ there is an absence of all subcerebral projection neurons and a complete lack of cortical projections to the brainstem or spinal cord. Our data shows that Satb2$^{-/-}$;Fezl$^{-/-}$ lack corpus callosum and have a disorganized striatum. Additionally, there is a complete loss of ctip2 positive layer V neurons while the ectopic upregulation of ctip2 in the upper layers is maintained. DiI experiments have shown that although the corticothalamic projections are present both in the Fezl$^{-/-}$ and Fezl$^{-/-}$;Satb2$^{-/-}$, the subcortical projections that are absent in the Fezl$^{-/-}$ are restored in the compound mutant. In Satb2$^{-/-}$;Ctip2$^{-/-}$ preliminary analysis shows a lack of corpus callosum indicating the presence of additional ectopically expressed molecules, except ctip2, that are responsible for misguiding the upper layer neurons to form subcortical connections.

61 LYSOSPHOSPHOLIPID ACID (LPA) CONTROLS AXONAL OUTGROWTH VIA PRG-1/RAS GRF-2 INTER-ACTION

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Plasticity Related Gene-1 (PRG-1) is a brain-specific membrane protein and the first identified member of the Plasticity Related Gene family (PRG-1-5).PRGs belong to the Lipid Phosphate/Phosphatase (LPP) superfamily whose members have an extracellular ectoenzymatic activity known to dephosphorylate lysophosphatidic acid (LPA) into its inactive monomers.PRG-1 is known to act specifically at the excitatory synapse on hippocampal neurons and has recently been proposed as an important player in the modulatory control of hippocampal excitability by means of non-enzymatic control of extracellular LPA concentration at the synaptic level.We have identified an interaction between the PRG-1 unique hydrophilic C-terminus and a Ras-specific exchange factor 2 (Ras GRF-2).This interaction takes place not only after overexpression of both proteins in mammalian cells, but also endogenous in primary neuronal culture. Furthermore, the endogenous PRG-1/Ras GRF-2 interaction is disrupted after extracellular LPA application.To assess the intracellular signaling cascade, phosphorylation of Mitogen Activated Protein Kinase (MAPK) was analyzed; enhanced MEK/ERK activation but no p38 phosphorylation was detected in primary neurons after LPA application.We also found that PRG-1 protein-protein interaction controls the intracellular levels of the active protooncogene N-Ras. Finally, significant axon elongation could be shown after increasing the N-Ras protein level in primary neurons. Thus, our research shows PRG-1 as a Ras-cascade controller depending on extracellular LPA presence.

Supported by NaFöGs,GRK1123,DFG(BR2345/1-1) and equipment is sponsored by the Sonnenfeld Stiftung.

62 STRONG INFILTRATION OF REGULATORY T CELLS INTO THE CNS 14 DAYS AFTER ENTORHI-NAL CORTEX LESION AND MIDDLE CEREBRAL ARTERY OCCLUSION

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Recent data suggest that inflammatory and regulatory T cells (Treg) in the brain participate in immune regulation after injury. To date, little is known about the exact mechanisms of the induction and infiltration time course of Treg after traumatic brain injury and ischemic stroke. Our study investigated the temporary infiltration and localization of Treg in the brain after entorhinal cortex lesion (ECL) and middle cerebral artery occlusion (MCAO). ECL and MCAO were performed in FoxP3EGFP transgenic mice, and Treg infiltration was analyzed by flow cytometry on days 7, 14, and 30 after surgery. Treg were identified by the expression of CD4 and Foxp3. Interestingly, the number of brain-infiltrating Treg peaked on day 14. An increase of Treg occurred in the CD4+/Treg ratio at days 14 and 30 compared to day 7 in the ipsilesional hemisphere of both models. Additionally, CD25 was downregulated in the Treg subset on days 7, 14 and 30, which raises the question whether proliferation or neogenesis of Treg takes place in the brain or periphery. In order to localize Foxp3+ T cells in the brain, cryosections were stained with antibodies against EGFP and laminin on day 14 after ECL and MCAO. Foxp3+ T cells were detected in both models directly within the necrotic area and in

the parenchyma adjacent to the lesion. Further investigations are in progress to differentiate between infiltration versus neogenesis and to determine the regulatory potential of the Treg after lesion.

63 THE EFFECT OF SODIUM-CAPRATE ON PLASMA MEMBRANE LOCALIZATION OF CLAUDIN-5

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The blood-brain barrier (BBB) is formed by endothelial cells and drug delivery is often poorly effective. Therefore, the treatment of several brain disorders remains inadequate. The paracellular cleft is tightened by tight junctions (TJ) where claudin-5 (Cld5) disables the paracellular permeability for molecules <800 Da. Cld5 interacts in the plasma membrane of the same cell (*cis*-interaction) and between plasma membranes of adjacent cells (*trans*-interaction). Thus, we are searching for small molecules which temporally open the BBB by targeting Cld5, in order to improve drug delivery into the brain. Sodium-caprate (C10) is known to open TJ. However, relatively high concentrations are needed to get a moderate effect. Furthermore, the mode of action is still unclear. Thus, we are characterising the interaction of claudin-5-YFP (yellow fluorescent protein) transfected HEK-293 (human embryonic kidney) cells under the influence of C10 using confocal microscopy. Due to the enrichment of Cld5 in membrane contacts between neighbouring cells expressing claudin-5-YFP (*trans*-interaction), the intensity of the YFP signal was clearly elevated compared to the cell contacts of non transfected cells, and remained unaffected after 60 minutes of investigation. The decreased YFP signal, following the treatment with C10, indicates a reduced *trans*-interaction of Cld5. Moreover, a concentration and time dependent effect was likely. HEK-293 cells stably transfected with claudin-5-YFP turned out to be a good model for testing small molecules which reduce the *trans*-interaction of Cld5. These findings can facilitate the investigation of modulators as potential openers of the BBB. In addition, preconditions for a high throughput-screening of small molecules to improve drug delivery to the brain are now available.

64 MINOCYCLINE ATTENUATES THE MICROGLIA-ASSISTED GLIOMA EXPANSION AND INVASION

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Gliomas are the most common form of brain tumors in humans. Invasion into the brain parenchyma is a hallmark of malignant gliomas and may explain the therapeutic failure and recurrence of the tumor after surgery and other forms of therapy. The process of invasion is facilitated by the secretion of several metalloproteases that degrade the extracellular matrix. Metalloproteases are released as inactive pro-forms that become activated upon cleavage by membrane anchored metalloproteases. Our group reported that membrane type 1 metalloprotease (MT1-MMP) is upregulated in glioma-associated microglia. Soluble factor(s) released from glioma cells triggered the expression and activity of MT1-MMP via the toll-like receptor and p38 MAPK signaling pathways (Markovic,D.,et al 2009). The microglial MT1-MMP activates glioma-derived pro-MMP-2 and promotes glioma diffusion. Currently, we are investigating the effect(s) of Minocycline, a second-generation derivative of the antibiotic tetracycline, on limiting microglia-assisted invasion of glioma cells into healthy brain under *in vitro* and *in vivo* conditions. We found that minocycline, a reported blocker of microglial activation and p38 MAPK signaling, interferes with and reduces the MT1-MMP expression and activity in glioma-associated microglia at the mRNA and protein levels. When Minocycline was administered to *ex vivo* organotypic brain slice cultures inoculated with glioma cells, a significant decrease in tumor expansion was observed. A similar pattern of tumor size reduction was also observed under *in vivo* conditions upon Minocycline administration to an experimental glioma mouse model, with a concomitant decrease in MT1-MMP expression. Our on-going and future experiments will thus aim to enhance a better understanding of the molecular mechanisms and efficacy of Minocycline as an adjuvant therapy to existing treatment modalities of gliomas.

65 REDUCED HYPERPOLARIZAT-ION-ACTIVATED CATION CURRENTS IN TEMPORAL LOBE EPILEPSY

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Hyperpolarization-activated cation currents (I_H, mediated by HCN channels) govern important parameters of neuronal excitability and have been implicated in epileptic disorders. Knock-out of subunit expression in mice induces spontaneous seizures ($HCN2^{-/-}$) or increases the suceptibility to the convulsant kainate ($HCN1^{-/-}$). In other animal models downregulations of the HCN1-mediated I_H component have been reported[1]. Little is known about the role of I_H in human epilepsy, we therefore investigated this current in neocortical pyramidal neurons (layer 2/3) in epilepsy surgery tissues with

patch-clamp recordings[2]. Recently we also began to measure the expression of HCN1 and HCN2 with quantitative RT-PCR. In tissues from patients with temporal lobe epilepsy (TLE) the I_H was smaller and activated more slowly than in frontal lobe epilepsy (FLE) cases (current densities TLE: 2.7 pA/pF, FLE: 4.7 pA/pF). Within the TLE group the I_H-density (averaged per patient) was 24% smaller in patients who had suffered many (weekly >2, average 7.5) complex partial seizures (CPS) than in the group with few (weekly <2, average 0.8) CPS. However, mRNA-levels of HCN1 (and HCN2) subunits were indistinguishable in these clinical groups despite different current densities. Pathophysiological impairment of HCN channel expression (and thus I_H function) can occur at the transcriptional level (e.g. in hippocampal neurons after entorhinal cortex lesion[3]) or at the translational level (e.g. in epilepsy-prone WAG/Rij-rats[1]). Our data suggest that in human TLE post-translational mechanisms may account for the deficits of neocortical I_H.

66 BETA-ADRENERGIC RECEPTOR ACTIVATION INDUCES LONG-LASTING POTENTIATION IN BURSTING BUT NOT REGULAR FIRING CELLS AT CA1-SUBICU-LUM SYNAPSES

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The hippocampus plays a central role in memory formation in the mammalian brain. Subicular neurons represent the principle target of the CA1 pyramidal cells and constitute the primary hippocampal output to various brain areas involved in memory storage. Pyramidal cells in the subiculum have been classified as bursting and regular firing cells. In this study we demonstrate that a single application of 2 μM isoproterenol (beta-adrenergic agonist) alone induces a long-lasting potentiation of responses to alveus stimulation in bursting but not regular firing cells. This effect is prevented by beta-adrenergic receptor antagonist propranolol (2 μM). The isoproterenol-induced potentiation in bursting cells does not depend on postsynaptic Ca^{2+}-signaling as BAPTA does not prevent its induction. Furthermore, paired-pulse facilitation reveals that the site of the expression of this potentiation is presynaptic. Our findings indicate that this cell-specific chemical form of long-term potentiation by activation of beta-adrenergic receptors contributes to the trafficking of hippocampal output onto subicular bursting cells.

67 BURST-LIKE SPIKE PATTERNS IN A RESONATE-AND-FIRE MODEL NEURON

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Stellate cells in the entorhinal cortex (EC) are likely to be the grid cells observed in behaving animals in vivo (Fyhn et al. 2004). They express a subthreshold resonance that favors subthreshold inputs in the theta range (8-15 Hz). Furthermore, stellate cells exhibit prominent subthreshold oscillations when depolarized, which may contribute to grid-like firing in-vivo (Burgess et al. 2007). Previously, it was shown that subthreshold resonance in these cells can lead to subthreshold oscillations and clustered spike patterns, which are not observed in nonresonant pyramidal neurons in EC layer III (Engel et al. 2008). In stellate cells, a combination of subthreshold resonance and additional spike-induced currents may hence lead to spiking responses that carry information in the resulting burst-like patterns. Here, we investigate in simple resonate-and-fire models how the interplay of the stimulus and subthreshold oscillations can give rise to bursts of spikes and how specific aspects of a stimulus are then encoded in the bursting responses.

Supported by the BMBF (BPCN and BCCN Berlin), DFG (SFB 618), and the Robert-Bosch Foundation.

68 GAMMA OSCILLATIONS WITHIN THE SUBICULUM IN VITRO

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The hippocampal circuit is capable of exhibiting *in vivo* and *in vitro* network oscillations at theta and gamma frequency range. Considering that the hippocampus and subiculum function as an integrated system crucial for memory and cognition, it is of interest to know whether similar network rhythms occur in hippocampal output structure – subiculum. We explored these issues in the present study using combined hippocampal–subicular–entorhinal cortex slices prepared from adult mice. Kainate (400 nM) was bath-applied to obtain field potential network oscillations. Extracellular recordings were obtained from stratum pyramidale of areas CA1, CA3, subiculum and superficial layers of the entorhinal cortex with ACSF-filled glass pipettes. Network gamma frequency oscillations were detected in all recorded areas. However, they were most frequently observed in the subiculum. In addition, the isolated subicular circuit could elicit network gamma frequency oscillations independent of entorhinal and hippocampal inputs. We suggest that the subicular

neuronal network is capable of generating on its own gamma oscillatory activity and that the subiculum functions as both a relay and an amplifier, spreading this activity from the hippocampus to the entorhinal cortex.

Supported by the SFB TR/B5 to TG

69 CLAUDIN-DERIVED PEPTIDES FOR MODULATION OF THE BLOOD-BRAIN BARRIER (BBB) PERMEABILITY

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The limitation of most pharmaceutical drugs to achieve the target tissue is the paracellular barrier formed by tight junctions (TJ). Therefore, the modulation of TJ integrity is a promising strategy to improve selective drug delivery. The integral membrane proteins of the claudin family contain four transmembrane helices, a cytosolic N- and C-terminus as well as two extracellular loops. The latter are directly involved in the paracellular barrier function of epithelial and endothelial cells. Moreover, claudin-claudin interactions can be sub-divided into *trans*- and *cis*-interactions, homophilically and heterophilically. It is suspected that the first and the second extracellular loop are involved in these interactions. Up to now, little is known about the mechanism in detail. The proof-of-concept for peptidic extracellular claudin-claudin inhibition has been demonstrated by the C-terminal region of the *clostridium perfringens* enterotoxin (C-CPE), which interacts specifically with the second extracellular loop of claudin-3 and claudin-4. Moreover, several peptides mimicing the extracellular loops of different claudin family members were investigated with respect to their influence of TJ integrity. Interestingly, the claudin-1 peptide (C1-C2) has been obtained as potential TJ modulator. In claudin-1 expressing Caco-2 cells, the transcellular electrical resistance (TER) was significantly reduced 24 hours after peptide treatment. This result offers the possibility for the successful application of claudin-derived peptides for selective TJ opening. Due to this knowledge, our work will focus on the development, characterization and optimization of peptidic TJ modulators to enhance the paracellular drug delivery, especially with respect to large molecules across the BBB. Furthermore, claudin-based peptides will give new insights into the extracellular homophilic and heterophilic interactions of claudins.

70 *TEASHIRT1* IS ESSENTIAL FOR THE DEVELOPMENT OF OLFAC-TORY BULB GRANULE CELL NEURONS

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The mammalian olfactory bulb constitutes the first relay station for processing of odor stimuli that are detected by sensory neurons located in the nasal olfactory epithelium. Forming initially as an evagination of the rostral telencephalic ventricular zone, the bulb becomes populated by neurons generated locally within the olfactory bulb ventricular zone, as well as at sites more distal within the telencephalon. Distally generated olfactory bulb neurons move tangentially in a rostral direction and must travel considerable distances to their destination, before assuming a radial mode of migration within the bulb itself. The mechanisms underlying the generation and migration of neural precursors into the adult olfactory bulb within the rostral migratory stream have received considerable attention in recent years. In contrast, the development of neural precursors that populate the embryonic olfactory bulb remain comparatively poorly understood. We present here a detailed characterisation of the cell populations within the granule cell layer of the embryonic mouse olfactory bulb, and assign to the zinc-finger homeodomain factor Teashirt1 (Tshz1) an essential role in both the radial migration and the molecular specification of early born, distally generated granule cell neurons. Early-born granule cell neurons arrived within the bulbs of *Tshz1*$^{-/-}$ mutant mice, but distributed aberrantly within the radial dimension, forming closely-packed cell aggregates. Within these clusters, cells of the Tshz1 lineage failed to express the zinc-finger transcription factors Sp8 and Sall3 and remained in an immature state as defined by the loss of expression of the markers neuN, glutamic acid decarboxylase (GAD)-67, g-amino butyric acid (GABA), tyrosine hydroxylase and guanine deaminase (cypin). Our analyses demonstrate that Tshz1 is essential for GABA-ergic and dopaminergic differentiation of olfactory bulb granule cell interneurons. Tshz1 is the first molecule to be characterised, which functionally distinguishes between the differentiation programs of olfactory bulb granule cell and periglomerular cell neurons. In addition, our analyses of *Tshz1*-/- mice indicate that soluble and/or cell surface factors produced by the Tshz1+ outer granule cell lineage regulate the spatial distribution of other granule cell neuron populations within the olfactory bulb.

71 MODULATIONS IN SUBTHALAMIC ALPHA ACTIVITY DURING EMOTIONAL PROCESSING CORRELATE WITH SEVERITY OF POSTOPERATIVE DEPRESSIVE SYMPTOMS IN PATIENTS WITH PARKINSON'S DISEASE

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STN-DBS is a very effective treatment in patients with advanced PD to improve motor symptoms. However, depressive mood changes have been described in PD patients after STN DBS. Here, we aimed to identify PD patients at risk to develop depressive symptoms during chronic STN-DBS using direct recordings of STN local field potential (LFP) activity at the time of electrode implantation. 13 PD patients were assessed for depressive symptoms using Beck Depression Inventory (BDI) at the time of STN macroelectrode implantation and at 3 months post-operative. A few days after electrode implantation, STN LFP-activity was recorded via the DBS electrodes during presentation of emotionally arousing stimuli (pleasant, unpleasant and neutral) from the International Affective Picture System. Based on previous results (Kühn et al. 2005) event-related desynchronisation (ERD) was calculated as changes in LFP alpha-power (8-12Hz) 1-2s after stimulus onset compared to baseline. Pearson correlation was used to test for a correlation between alpha-ERD and depressive symptoms. The alpha ERD in unpleasant trials negatively correlated with the individual BDI scores at 3 months post-operatively ($r=-0.826$, $p=0.006$). Thus, the larger the ERD to unpleasant stimuli at the time of operation the more depressive symptoms were present post-operatively. The alpha-ERD in pleasant trials correlated positively with the BDI at the time of operation ($r=0.726$, $p=0.017$) but did not reach statistical significance at 3 months post-operative ($r=0.519$, $p=0.152$). Electrophysiological marker such as the subthalamic alpha-ERD may potentially be used to estimate depressive disturbances in PD patients with chronic STN-DBS at an early stage when patients have not yet become clinically depressed.

72 ALPHA-ADRENORECEPTOR ACTIVATION SUPPRESSES SHARP WAVE-RIPPLE ACTIVITY IN RAT HIPPOCAMPAL SLICES

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Norepinephrine (NE) has been shown to facilitate learning and memory by modulating synaptic plasticity in the hippocampus *in vivo*. During memory consolidation, transiently stored information is transferred from the hippocampus into the cortical mantle. This process is believed to depend on the generation of sharp wave-ripple complexes (SPW-Rs), during which previously stored information might be replayed. Here, we used rat hippocampal slices to investigate neuromodulatory effects of NE on SPW-Rs, which were induced by a standard long-term potentiation (LTP) protocol. NE (10-50 ìM) dose-dependently and reversibly suppressed SPW-Rs via activation of a1 adrenoreceptors, as indicated by similar effects of phenylephrine (100 ìM). Suppression of SPW-Rs by NE was associated with a moderate hyperpolarization in the majority of CA3 pyramidal cells. However, the abrupt NE- mediated suppression of SPW-Rs was presumably due to modulatory effects on presynaptic terminals of CA3 pyramidal cells. This was indicated by activity- dependent changes in [Ca2+]o and Ca2+ fluorescence signals attributed to presynaptic Ca2+ uptake, paired pulse ratio of evoked EPSPs and coefficient of variance analyses. Together, our data indicate that the NE-mediated suppression of hippocampal SPW-Rs depends on a1 adrenoreceptor activation.

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/Transregio 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 – as well as neurodegenerative disorders such as Alzheimer's disease.
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.

Spokesmen: Prof. Dr. Frank Heppner (Berlin)
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GRK 1123
„Cellular Mechanisms of Learning and Memory Consolidation in the Hippocampal Formation“

The formation of explicit memory is one of the most important aspects of human behavior and the prerequisite for our individuality. Conversely, disturbance of the cellular and molecular processes underlying learning and memory can result in a variety of neurological and psychiatric disorders such as temporal lobe epilepsy and Alzheimer's disease. Each of the 13 tutors of this graduate school will bring to these problems his or her specific expertise. Using physiological, morphological, cell biological, genetic, and behavioral methods, as well as modeling of neuronal network properties, the students in the graduate school will have the opportunity to contribute to this exciting field of the neurosciences within an excellent environment for training in modern neurobiological methods.

Spokesmen: Prof. Dr. med. Uwe Heinemann
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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.

Spokesperson: Prof. Dr. Helmut Kettenmann

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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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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.

Spokespersons: Prof. Dr. Matthias Endres
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CSB
Center for Stroke Research Berlin

Research Unit: DFG Forschergruppe 778 "Conflicts as Signals in Cognitive Systems"

The general goal of the research group on "Conflicts as Signals in Cognitive Systems" proceeds from the assumption 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 nonrelevant memory representations).

Subprojects:

Tanja Endrass & Norbert Kathmann (Humboldt-Universität): Functional and Structural Dissociation of Performance Monitoring of Incorrect and Correct Reactions

Peter Frensch (Humboldt-Universität): Conflicts as Triggers for Optimizing Strategies

Kerstin Irlbacher & Stephan Brandt (Charité): Adaptive Cognitive Controll during Conflict Processing

Arthur Jacobs (Freie Universität): Modellgeleitete neurokognitive Analyse lexiko-semantischer und orthographisch-phonologischer Konflikte beim impliziten und expliziten Wiedererkennen.

Shu-Chen Li, Ulman Lindenberger, & Hauke Heekeren (Max Planck Institute for Live-Span Development): Neuromodulation of Cognitive Monitoring across Adult Development: A Genomic Imaging Project

Birgit Stürmer (Humboldt-Universität): On the Specificity and Intentionality of Adaptations Triggered by Conflicts

Oliver Wilhelm (Humboldt-Universität) & Klaus Oberauer (University of Zurich): Individual Differences in Solving Cognitive Conflicts, Conflicts in Gambling Tasks, and Conflicts in Delay of Gratification Tasks as Determinants of School Outcomes

Spokespersons: Prof. Dr. Peter Frensch, Dr. Birgit Stürmer, Prof. Dr. Stephan Brandt

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Conflicts as Signals in Cognitive Systems

Cluster of Excellence (XC 257) "NeuroCure: towards a better outcome of neurological disorders."

NeuroCure – *Towards a better outcome of neurological disorders* - was identified in October 2007 as an internationally visible and competitive neuroscience cluster of excellence at the Charité – Universitätsmedizin Berlin in a nationwide competition of excellence initiatives of the German federal and state governments. With financing of over 50 million Euros until the year 2012, the interdisciplinary consortium focuses on researching neurological disease mechanisms and the transfer – or *translation* – of knowledge from basic science to clinical practice.
NeuroCure's substantial funding will be used by the partner institutions Humboldt-Universität zu Berlin, Freie Universität Berlin, and non-university research institutions Max-Delbrück-Centrum für Molekulare Medizin (MDC), Leibniz Institut für Molekulare Pharmakologie (FMP) and Deutsches Rheuma-Forschungszentrum Berlin (DRFZ) to expand the well-established neuroscience community by both strengthening the network of current research activities and establishing 17 new professorships.
With the goal of transferring - to an even greater extent than before - insights gained from basic science to clinical studies and of developing new therapies, NeuroCure is active primarily in the areas of cerebrovascular diseases, neuroinflammation and disturbances of functional network structures, and in particular with the diseases stroke, multiple sclerosis, epilepsy and developmental disturbances. The focus is not only on the underlying disease mechanisms common to these afflictions but also on the overarching research approach and concept. NeuroCure addresses these topics in six thematic research areas. In addition, the cluster of excellence is expanding various clinical and technological infrastructures with central know-how that can be shared by all scientists.

Speaker: Prof. Dietmar Schmitz

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NEUROCURE
Cluster of Excellence

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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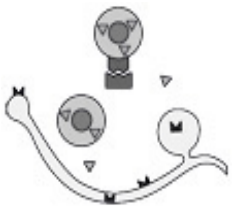

Interdisciplinary Wolfgang Köhler Research Center

This interdisciplinary research center at the Humboldt-Universität zu Berlin integrates psychology, biology, computer sciences, linguistics, and neurosciences. Studying conflicts unites researchers from Humboldt-Universität zu Berlin, Freie Universität Berlin, Charité-Universitätsmedizin Berlin, and Max-Planck-Institute for Human Development Berlin. This interdisciplinary center was founded in September 2007 and aims at advancing the understanding of intelligent systems. The center will render a significant contribution to the life sciences at the interface of psychological and computational cognitive sciences, neurosciences, psychiatrics, biology, and linguistics. Within individual projects, experimental psychological approaches are combined with neuroscientific methods. Our investigations have three main aspects:

Origins of conflicts: Research on conflicts within the cognitive system of humans distinguishes between conflicts of codes and conflicts of resources. Code conflicts result from discrepancies between internal mental representations and can originate at different internal processing stages. Resource conflicts, by contrast, are due to several processes competing for restricted resources for their task accomplishment.

Monitoring of conflicts: Several projects investigate how the mental system monitors for potential occurrence of conflicts, and how conflicts are identified and evaluated. We study whether conflict monitoring is a uniform and domain-independent process of action planning, or whether different monitoring processes are integrated into specialized neurocognitive control networks.

Consequences of conflicts: Often conflicts do have consequences. Thus, they can lead to changes of the system itself aiming at avoiding future conflicts revealing the adaptive potential inherent in conflicts. Our research aims both at interpersonal and intra-individual conflicts.

Subprojects by: Jens Asendorpf (HU), Stephan Brandt (Charité), Hans-Dieter Burkhard (HU), Peter Frensch (HU), Peter Hammerstein (HU), Hauke Heekeren (FU and Max-Planck-Institute for Human Development), Andreas Heinz (Charité), Arthur Jacobs (FU), Norbert Kathmann (HU), Manfred Krifka (HU), Carola Lehle (HU), Shu-Chen Li (Max-Planck-Institute for Human Development), Ulman Lindenberger (Max-Planck-Institute for Human Development), Beate Meffert (HU), Annekathrin Schacht (HU), Thorsten Schubert (HU), Werner Sommer (HU), Wolfgang Scholl (HU), Birgit Stürmer (HU), Oliver Wilhelm (HU)

Spokesperson: Prof. Dr. Norbert Kathmann

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Interdisciplinary Wolfgang Köhler Research Center
Conflicts in Intelligent Systems

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. 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.

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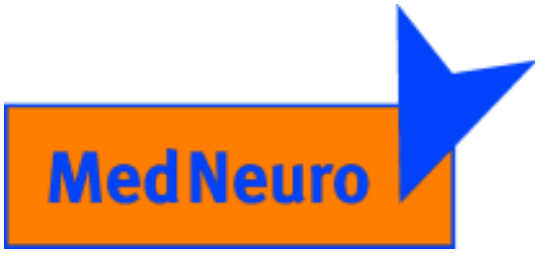

Bernstein Center for Computational Neuroscience Berlin

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, Max-Delbrück-Zentrum and Universität Potsdam. 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 also in the second funding period from 2010-2015. 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 accredited Master Program runs for 2 years and is taught by the faculty of the BCCN Berlin. It is by now in its fourth year. The PhD Program started in 2007and is financially supported by the new Training Research Group 1589/1 "Sensory Computation in Neural Systems".

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Berlin School of Mind and Brain

The Berlin School of Mind and Brain is an international research school. Founded in 2006 as part of Germany's Excellence Initiative, it offers a three-year interdisciplinary doctoral program in English in the mind/brain sciences.
Research within the School focuses on the interface between the humanities and the neurosciences. Of particular interest are research areas that fall on the borders between the mind sciences (e.g., philosophy, linguistics, behavioral and cognitive science, economics), and the brain sciences (e.g., neurophysiology, computational neuroscience, neurology, psychiatry, and neurobiology). Major topics of research within the program include: 'conscious and unconscious perception', 'decision-making', 'language', 'brain plasticity and lifespan ontogeny', 'mental disorders and brain dysfunction', 'philosophy' (philosophy of mind and ethics), and molecular and cellular approaches to cognition (e.g. 'social cognition' and 'autism').
The School has a faculty comprised of 60 distinguished researchers, including five Max Planck directors. Hosted by the Humboldt University, the School's research program includes scientists from the Free University, the Charité, the Technical University, the Bernstein Center for Computational Neuroscience, and the Max Planck Institute for Human Development, as well as the Max Planck Institute for Human Cognitive and Brain Sciences in Leipzig and the universities of Leipzig, Potsdam, and Magdeburg.
Each year the School accepts ten to fifteen doctoral candidates into its program. Throughout the first half of the three-year program students attend eight one-week teaching weeks with relevance to the mind/brain research topics of the School, international lecture series, journal and methods clubs, poster presentations, and conferences of their choice. They are obliged to take a number of academic soft-skill courses such as presentation skills, grant-application writing, scientific writing, and are offered dissertation coaching, mentoring, and career advice.

Spokespersons: Prof. Dr. Michael Pauen, Prof. Dr. Arno Villringer

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Keywords

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