Program Abstracts

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The Berlin Neuroscience Forum 2012 is a joint activity of

SFB „"Theoretische Biologie"

SFB „Entwicklungsstörungen im Nervensystem"

SFB Transregio „Gehirn als Ziel von entzündlichen Prozessen"

SFB „Einrüstung von Membranen - Molekulare Mechanismen und zelluläre Funktionen"

GRK „Zelluläre Mechanismen von Lernen und Gedächtniskonsolidierung hippocampaler Funktion"

GRK „Neuropsychiatrie und Psychologie des Alters"

Zentrum für Schlaganfallforschung (CSB)

DFG-Forschergruppe „Konflikte als Signale"

DGF-Forschergruppe „"Biogenic amines in insects: coordination of physiological processes and behaviour"

Exzellenzcluster NeuroCure

Exzellenzcluster Language of Emotion

Studiengang „Medizinische Neurowissenschaften"

Promotionskolleg „Computational Neuroscience"

Bernstein Center for Computational Neuroscience

Berlin School of Mind and Brain

Berlin Neuroimaging Center

Helmholtz International Research School ‚Molecular Neurobiology' (MDC)

Leibniz-Institut für Molekulare Pharmakologie

Deutsches Zentrum für Neurodegenerative Erkrankungen - Cluster Berlin

Helmholtz Virtual Institute „Multifunctional Biomaterials for Medicine"

BMBF Network „ImmunoPain"

BMBF Network „Medical Systems Biology - Nociceptor Inhibition"

Program Committee

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Homepage

http://bnf2012.glia.mdc-berlin.de

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Registration	Thursday, July 05, 2012	11.00 - 13.00
Office Hours	Thursday, July 05, 2012 Friday, July 06, 2012	11.00 - 19.30 8.30 - 16.00
Office Phone	0160 902 18 506	
Poster Boards	Height : 120 cm Width: 100 cm	
Poster Sessions	Poster Session I Poster No. 1- 45 Thursday, July 05, 2012 !!! Posters must be removed immediately after the poster session on Thursday !!!	15.20 - 17.30
	Poster Session II Poster No. 46 - 90 Friday, July 06, 2012	13.00 - 15.00
Duration of Oral Presentations	Invited Speakers	45 min (talk) 15 min (disc.)
	Welcome to Berlin Sessions	20 min (talk) 10 min (disc.)
	Oral Presentations	10 min (talk) 5 min (disc.)

Scientific Program

Thursday, July 05, 2012

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:N.N.

Benedikt Grothe
(Department Biology II, Ludwig-Maximilians-University Munich, Germany)
BETWEEN MICROSECOND PRECISION AND CONTEXT DEPENDENT ADAPTATION - NEW INSIGHTS INTO BINAURAL PROCESSING AND ITS DYNAMICS

14.05 – 15.20	Oral Presentations Session I Chair: Oliver Peters

Nikolaus Berndt
Institute of Biochemistry,
BRAIN ENERGY METABOLISM AND NAD(P)H FLUO RESCENCE: INSIGHTS FROM MATHEMATICAL MODEL LING

Eleonora Franzoni
(Institute for Anatomy, Cell and Neurobiology, Charité–Universitätsmedizin, Berlin)
MIR-128: A PLEIOTROPIC REGULATOR OF NEURONAL TRANSLATION

Moritz Gröschel
(HNO-Klinik, Unfallkrankenhaus Berlin)
NOISE-INDUCED NEUROPLASTICITY IN THE CENTRAL AUDITORY SYSTEM

Thursday, July 05, 2012

Philipp Mergenthaler
(Deptartment of Experimental Neurology, Charité, Berlin)
HEXOKINASE II-MEDIATED HYPOXIA TOLERANCE – A MOLCULAR SWITCH GOVERNING CELLULAR FATE DEPENDING ON THE METABOLIC STATE.

Lisa Katharina Joachim
(Department of Psychiatry, Charité - CBF, Berlin)
INFLUENCE OF CLASSICAL BIOMARKERS ON COGNI TIVE OUTCOME IN A CLINICAL TRIAL

15.20 - 17.30 Poster Session I and Coffee Break

17.30 - 18.30 Welcome to Berlin Session I
Chair: Gabriel Curio

Christine Heim
(Institute of Medical Psychology, Charité University Medicine - Berlin, Germany
THE CONTRIBUTION OF EARLY-LIFE STRESS TO THE NEUROBIOLOGY OF DEPRESSION

Katharina von Kriegstein
(Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany)
NEURAL MECHANISMS OF HUMAN COMMUNICATION

18.30 - 19.30 Lecture II
Chair: Dietmar Schmitz

Istvan Mody
(The David Geffen School of Medicine at UCLA, Los Angeles, USA)
INSIGHTS INTO MECHANISMS OF STROKE AND FUNCTIONAL RECOVERY

19.30 - 21.00 Dinner

Friday, July 06, 2012

8.00 – 9.00	Breakfast
9.00 – 10.00	Lecture III Chair: Jens Dreier
	Ray Dolan *(Wellcome Trust Center for Neuroimaging, London, UK)* MOTIVATIONAL VALUE IN THE HUMAN BRAIN
10.00 – 11.00	Welcome to Berlin Session II Chair: Rosemarie Grantyn
	Britta J Eickholt *(Cluster of Excellence NeuroCure and Institute of Biochemistry, Charité Universitätsmedizin Berlin, Germany)* IT'S NOT ALL LIPIDS: A PI3K INDEPENDENT ROLE FOR THE PTEN TUMOUR SUPPRESSOR AT THE CENTRAL NERVOUS SYSTEM SYNAPSE
	Imre Vida *(Cluster of Excellence NeuroCure, Center for Anatomy, Institute for Integrative Neuroanatomy, Charité, Berlin)* FAST AND SLOW INHIBITORY INTERACTIONS AMONG GABAERGIC INTERNEURONS IN HIPPOCAMPAL NET WORKS
11.00 - 11.30	Coffee Break
11.30 - 12.30	Oral Presentations Session II Chair: Ulrich Dirnagl
	Alessandro Prigione *(Department of Vertebrate Genomics, Max Planck Institute for Molecular Genetics, Berlin)* MODELING MITOCHONDRIAL DNA ENCEPHALOPA THIES USING HUMAN INDUCED PLURIPOTENT STEM (IPS) CELLS

Sergej Rot
(Experimental Neurosurgery, Charité, Berlin)
CHARACTERIZATION OF MICROGLIA IN THE PERIVASCULAR NICHE OF GLIOBLASTOMA MULTIFORME

Maria Pannell
(Cellular Neurosciences, Max Delbrück Center for Molecular Medicine (MDC), Berlin)
RESPONSES OF ADULT AND NEONATAL MICROGLIA IN VITRO TO NEUROTRANSMITTERS/HORMONES AFTER ACTIVATION WITH LPS, IFN-GAMMA AND IL-4

Stephanie Wegener
(Neuroscience Research Center, Charité Berlin)
BREAKING THE SILENCE: A CRITICAL ROLE FOR PROSAP1/SHANK2 IN SYNAPTIC MATURATION

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Chair: Frank Heppner

Mathias Jucker
(Department of Cellular Neurology, Hertie-Institute for Clinical Brain Research and German Center for Neurodegenerative Diseases (DZNE), Tübingen, Germany)
PRION-LIKE ASPECTS OF ALZHEIMER PATHOLOGY

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AG Psychophysiology, Freie Universität Berlin and Technische Universität Berlin

2.PSYCHOPHYSICAL MEASUREMENTS OF DISCRIMINATION THRESHOLDS WITH SPECTRAL LIGHT SYNTHESIZERS
Krensel, A.; Backhaus, W.G.K.
AG Psychophysiology, Freie Universität Berlin and Technische Universität Berlin

3.TIME COURSES OF CHROMATIC ADAPTATION AND HELSON-JUDD COLOR SHIFTS
Burmeister, S.; Backhaus, W.G.K.
AG Psychophysiology, Freie Universität Berlin and Technische Universität Berlin

4.ROLE OF MICROGLIA IN NEUROGENESIS
BAUFELD, C.; MILLER, K.
INSTITUT FOR NEUROPATHOLOGY, CHARITÉ BERLIN

5.SYNAPTIC TAGGING MIGHT UNDERLIE ACTIVITY-DEPENDENT FORMATION OF DISTINCT NEURONAL ENSEMBLES IN THE RAT HIPPOCAMPUS IN VITRO
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Institute for Neurophysiology, Charité - Universitätsmedizin Berlin

6.SCAFFOLDING PROTEIN FUNCTION IN THE OLFACTORY SYSTEM
Bintig, W.; Baumgart, S.; Dooley, R.; Spehr, M.; Neuhaus, E.M.
Neurowissenschaftliches Forschungszentrum – NeuroCure

7.FUNCTION OF CLAUDIN-3 IN BRAIN CAPILLARIES UNDER HYPOXIC CONDITIONS
Blasig, R.; Helms, H. C.; Manchalu, S.; Müller, D.; Blasig, I.E.
AG Molekulare Zellphysiologie, Leibniz-Institut für Molekulare Pharmakologie

8.SENSITIVITY OF HYPOTHALAMIC NEURONS IN BIRDS ON DIFFERENT GLUCOSE AND LEPTIN CONCENTRATIONS
Bogatyrev, S.; Tzschentke; B.
Institute of Biology, WG Perinatal Adaptation, Humboldt-University of Berlin

9.NEURONAL BHLH PROTEINS NEX AND NDRF REGULATE CORTICAL COMMISSURE FORMATION PRIOR TO MIDLINE INTERACTIONS
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Institute of Cell Biology and Neurobiology, NeuroCure Cluster of Excellence, Charité – Universitätsmedizin Berlin

10. PATHWAY OF C-TERMINAL REGION OF THE CLOSTRIDIUM PERFRINGENS ENTEROTOXIN TROUGH CLAUDIN-3 EXPRESSING CELLS
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Molecular cell physiology and cell biology, Leibniz Institut für Molekulare Pharmakologie

11. PRO-INFLAMMATORY ENDOTOXIN ALTERS THE DYNAMICS OF MITOCHONDRIAL TRANSPORT IN NEURONS
Bros, E.; Niesner, R.; Paul, F.; Infante Duarte,C.
Experimental Neuroimmunology, Charité - Universitätsmedizin Berlin

12. DIRECT DIFFERENTIATION OF HUMAN IPS CELLS INTO SELF-RENEWING NEURAL PROGENITORS BY SMALL MOLECULES
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Anaesthesiologie, Charite, Campus Benjamin Franklin

14. TRAIL-EXPRESSING NK CELLS ARE NOT BENEFICIAL IN THE MOUSE MODEL OF MULTIPLE SCLEROSIS
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Experimentelle Neuroimmunology, Charité Universitätsmedizin

15. GENETIC MODELS FOR THE STUDY OF LIN41, A STEM CELL REGULATOR OF THE MIRNA PATHWAY
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Institut for Cell Biology and Neurobiology, Charité Universitätsmedizin

16. FUNCTIONAL SYNAPTIC CONNECTIVITY BETWEEN LAYER 2 CORTICAL EXCITATORY AND INHIBITORY NEURONS IN VIVO
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Department of Neuroscience, Max-Delbrück-Center for Molecular Medicine, Berlin-Buch

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Synaptic Dysfunction Group, Charité – Neurocure

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Department for Experimental Neurology, Charité Berlin

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Neurophysiologie, Charité

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Neurology, Charité

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Experimental Neurology, Charité Universitätsmedizin

22. SMALL MOLECULE MEDIATED CONVERSION OF TOXIC OLIGOMERS TO NON-TOXIC AMYLOID FIBRILS
Bieschke, J.; Herbst, M.; Wiglenda, T.; Friedrich, R.P.; Böddrich A.; Wanker, E.E.
AG Neuroproteomics, Max-Delbrück-Center for Molecular Medicine Berlin-Buch

23. NOISE INDUCED APOPTOTIC MECHANISMS IN THE CENTRAL AUDITORY PATHWAY
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Klinik für Hals- Nasen- Ohrenheilkunde, Unfallkrankenhaus Berlin

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Center for Stroke Research, Charité University Medicine Berlin

25. INTERNALISATION OF CLAUDIN-1 AND -5
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Molecular Physiology and Cell Biology, Leibnitz Institut für Molekulare Pharmakologie Berlin-Buch

26. GATING OF HIPPOCAMPAL OUTPUT BY BETA-ADRENERGIC RECEPTOR ACTIVATION
Grosser, S.; Gilling, K.E.; Hollnagel, J.- O., Behr, J.
Department of Neurophysiology, Charite

27. ARC/ARG3.1 COUPLES SYNAPTIC TRAFFICKING TO THE ENDOPLASMIC RETICULUM
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Center for Molecular Neurobiology Hamburg (ZMNH)

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Theoretical Biology, BCCN

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Neurophysics Group, Department of Neurology, Charité – Universitätsmedizin Berlin

30. THE ROLE OF MICROGLIAL TLR2 IN MICROGLIA-GLIOMA INTERACTION
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Cellular Neuroscience, Max Delbrueck Center for Molecular Medicine Berlin-Buch

31. PHYSIOLOGICAL ROLE OF HIGH FREQUENCY OSCILLATIONS IN THE HUMAN GLOBUS PALLIDUS INTERNUS
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Department of Neurology, Charité - Universitätsmedizin Berlin

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Center for Anatomy, Institute of Cell Biology

33. CDK5RAP2 EXPRESSION DURING MURINE AND HUMAN BRAIN DEVELOPMENT
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Center of Anatomy, Charité, Institute of Cell Biology and Neurobiology

34. EFFECTS OF SUDDEN UNILATERAL DEAFNESS ON BILATERAL SPIRAL GANGLION CELL DENSITY
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Institut für Biologie, HU Berlin

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, NeuroCure Clinical Research Center, Charité – Universitätsmedizin Berlin

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Kang, E.- J.; Major, S.; Jorks, D.; Friedman, A.; Dreier, J.P.
Center for Stroke Research Berlin, Charité University Medicine Berlin

37. ENDOGENOUSLY ACTIVATED P2 RECEPTORS MEDIATE MINOR MODULATORY EFFECTS ON EPILEPTIFORM ACTIVITY IN RAT MEDIAL ENTORHINAL CORTEX
Klaft, Z.J.; Schulz, S.B.; Maslarova, A.; Gabriel, S.; Heinemann, U.; Gerevich, Z.
Institute of Neurophysiology, Charité Universitätsmedizin Berlin

38. IDENTIFICATION OF NOVEL NEURONAL JNK TARGETS
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Neurowissenschaftliches Forschungszentrum (NWFZ), Charité, CCM

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Institut für Theoretishe Physik, Technische Universität Berlin

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Institute of Neurophysiology, Charité Universitätsmedizin Berlin

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Deptartment of Developmental Neurobiology, Max Delbrück Center for Molecular Medicine Berlin-Buch

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Institute of Neurophysiology, Charité Universitätsmedizin Berlin

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Insitute of Chemistry and Biochemistry, Freie Universität Berlin

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Department of Biological and Medical Sciences - Faculty of Health and Life Scien, Oxford Brookes University

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Institute for Integrative Neuroanatomy, Charité University Medicine

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Zentrum für Anatomie, Institut für Integrative Neuroanatomie

47. NEUROTRANSMITTER TRANSPORTERS - WHAT THEY LOVE AND HATE
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Charité - Centre for Anatomy, Institute for integrative Neuroanatomy

48. SPIKELETS IN HIPPOCAMPAL CA1 PYRAMIDAL NEURONS: ORIGIN AND FUNCTIONAL IMPLICATIONS
Michalikova, M.; Kempter, R.
Institute for Theoretical Biology, Humboldt-Universität zu Berlin

49. IRON OXIDE MAGNETIC NANOPARTICLES REVEAL EARLY EVENTS IN CENTRAL NERVOUS SYSTEM INFLAMMATION
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Experimental Neuroimmunology, Charité-Universitätmedizin Berlin

50. MODELING OF THE THETA RHYTHM PATTERNS IN SEPTO-HIPPOCAMPAL AREA
Milster, S.; Lavrova, A.; Schimansky-Geier, L.
Institut für Physik, Humboldt-Universität zu Berlin

51. VISUALIZING MIGRATING MONOCYTES WITH VERY SMALL SUPERPARAMAGNETIC IRON OXIDE PARTICLES AFTER ENTORHINAL CORTEX LESION WITH MRI
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Charité Universitaetsmedizin Berlin, Institute for Cell Biology and Neurobiology

52. THE (BETA)(+)(ALPHA)(-) INTERFACES OF (ALPHA4BETA2)2ALPHA4 NICOTINIC RECEPTORS CONTRIBUTE TO RECEPTOR FUNCTION.
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Department of Biological and Medical Sciences - Faculty of Health and Life Scien, Oxford Brookes University

53. MLIN41 REGULATES THE MIRNA PATHWAY
Nguyen, D.; Wulczyn, F. G.
Institute for Cell and Neurobiology, Centre for Anatomy, Charité –Universitätsmedizin Berlin

54. AMPLITUDE DYNAMICS IN CORTICOSPINAL INTERACTIONS
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Department of Neurology, Charité - University Medicine Berlin

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NeuroCure Clinical Research Center, Charité Berlin

56. RESPONSES OF ADULT AND NEONATAL MICROGLIA IN VITRO TO NEUROTRANSMITTERS/HORMONES AFTER ACTIVATION WITH LPS, IFN-GAMMA AND IL-4
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Cellular Neuroscience, Max-Delbrück-Center for Molecular Medicine Berlin-Buch

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Cortical Development Group, Cell and Neurobiology, Center for Anatomy

58. SYNAPTIC PATTERNS IN THE STRIATUM OF NORMAL AND R6/2 MICE, A MODEL OF HUNTINGTON'S DISEASE
Paul, S.; Sukchev, M.; Rosemarie Grantyn, R.
Synaptic Dysfunction Group, Charité – Neurocure

59. THE INFLUENCE OF FILTERING ON THE EXTRACTION OF WHITE MATTER FIBER BUNDLES FROM DIFFUSION TENSOR IMAGING DATA
Perkunder, H.; Ivanova, G.
Department of Computer Science, Humboldt-Universität zu Berlin

60. INDUCING CORTICAL OUTGROWTH: A NEW IN VITRO TECHNIQUE TO STUDY NEURONAL REGENERATION IN MOTOR CORTEX – SPINAL CORD COCULTURES
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Institute of Cell Biology and Neurobiology, Center for Anatomy, Charité-Universitätsmedizin Berlin

61. DIFFERENTIAL PROCESSING OF SENSORY INPUT BY NEIGHBOURING LAYER 2 PYRAMIDAL NEURONS IN WHISKER BARREL CORTEX REVEALED BY IMMEDIATE-EARLY-GENE EXPRESSION
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Neuroscience, MDC

62. ANALYSIS OF PROTEIN-PROTEIN INTERACTIONS USING SPLIT-EYFP PROBES: FOCUS ON PSD-ASSOCIATED PROTEINS
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63. PROTEIN KINASE C MODULATES IH – A PUTATIVE LINK BETWEEN INTERFERON SIGNALING CASCADE AND HYPERPOLARIZATION-ACTIVATED, CYCLIC NUCLEOTIDE-GATED (HCN) CHANNELS
Reetz, O.; Stadler, K.; Strauss, U.
Institute of Cell- and Neurobiology, Charité

64. THETA-PHASE CODING IN THE MEDIAL ENTORHINAL CORTEX
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Institute for Theoretical Biology, Humboldt-University Berlin

65. BLOCKING STROKE-INDUCED IMMUNODEPRESSION (SIDS) DOES NOT LEAD TO AGGRAVATED AUTOIMMUNE RESPONSE AGAINST THE CNS PROTEINS
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Department of Experimental Neurology,

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Theoretical Biology, Humboldt University

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Neuropathology, Charité Universitätsmedizin Berlin

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Schregel, K.; Wuerfel, J.
Institute of Neuroradiology, University Luebeck, Ratzeburger Allee 160, 23538 Luebeck, Germany

69. LPA1, LPA2, AND LPA4 RECEPTOR EXPRESSION DURING MOUSE BRAIN DEVELOPMENT
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Institute for Cell and Neurobiology, Charité Berlin

70. SYNAPTOPHYSIN - MASKING GENDER DIFFERENCES IN NEURONAL PLASTICITY?
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Centre for Anatomy, Institute of Integrative Neuroanatomy, Charité – Universitätsmedizin Berlin

71. THE IMPACT OF PRIOR KNOWLEDGE ON OBJECT SEARCH IN REAL-WORLD SCENES
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Department of Neurology, Campus Benjamin Franklin, Charité-University-Medicine Berlin

72. FUNCTIONAL ANALYSIS OF THE SINGLE NUCLEOTIDE POLYMORPHISMS (SNPS) IN THE CODING REGION OF THE BETA4 SUBUNIT OF NACHR
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Molecular Neurobiology, Max-Delbrück-Center for Molecular Medicine Berlin-Buch

73. ROLE OF SIP1 IN ORCHESTERATING NEOCORTICAL CONNECTIVITY
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Cortical Development Group, Institute for cell and Neurobiology

74. AT BIRTH THE HYPERPOLARIZATION-ACTIVATED CYCLIC NUCLEOTIDE-GATED (HCN)1 SUBUNIT DOES NOT CONTRIBUTE TO RODENT NEOCORTICAL IH
Stoenica, L.; Battefeld, A.; Bräuer, A.U.; Strauss, U.

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Department of Experimental Neurology, Charité Universitätsmedizin Berlin

76. WHOLE-CELL RECORDINGS FROM MOUSE FORELIMB MOTOR CORTEX NEURONS DURING TARGETED REACHING
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77. LARGE-SCALE NEURAL MODEL OF FUNCTIONAL CONNECTIVITY BETWEEN ANATOMICALLY UNCONNECTED AREAS OF THE HUMAN CORTEX
Vuksanovic, V.; Hövell, P:
Bernstein Center for Computational Neuroscience Berlin

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79. PRE-SYMPTOMATIC CEREBELLAR LESIONS AND VENTRICLE ENLARGEMENT IN AN EAE MOUSE MODEL REVEALED BY MICROSCOPIC MRI
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80. CHARACTERIZING THE MITOCHONDRIAL HKII-DEPENDENT MULTIPROTEIN COMPLEX USING BIMOLECULAR FLUORESCENCE COMPLEMENTATION (BIFC) AND A PROXIMITY LIGATION ASSAY (PLA)
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Experimental Neurology, Charité

81. THE IMPACT OF FOCAL CEREBRAL ISCHAEMIA ON THE COMPOSITION OF MURINE INTESTINAL MICROBIOTA
Winek, K.; Engel, O.; Meisel, A.; Dabrowski, P.W.; Radonic, A.; Nitsche, A.; Rex, A.; Dirnagl, U.
Department of Experimental Neurology, Charité – Universitätsmedizin Berlin

82. IMPAIRED NEUROVASCULAR COUPLING TO ICTAL EPILEPTIC ACTIVITY AND SPREADING DEPOLARIZATION IN A PATIENT WITH SUBARACHNOID HEMORRHAGE
Winkler, M.K.L; Chassidim,Y.; Revankar, G.S.; Major, S.; Kang, E.J.; Oliveira-Ferreira, A.I.; Woitzik, J.; Scheel, M.; Friedman, A.; Dreier, J.P.
Center for Stroke Research, Charité Universitätsmedizin Berlin

83. REDUCTION OF TONIC ACTIONS OF AMBIENT GABA IN THE STRIATUM: DATA FROM AN ESTABLISHED (R6/2) AND A VERY RECENT (Q175) MODEL OF HUNTINGTON'S DISEASE (HD)
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Synaptic Dysfunction Group, Charité – Neurocure

84. MOLECULAR MECHANISMS OF NEUROD2/6 FUNCTIONS IN NEOCORTICAL DEVELOPMENT
Yan, K.; Bormuth, I.; Schwab, M.; Nave, K.A.; Tarabykin, V.
Institute of Cell and Neurobiology, Center of Anatomy, Charité - Universitätsmedizin Berlin

85. DYNAMICAL SWITCHING BETWEEN HIPPOCAMPAL NETWORK STATES: ROLE OF INTERNEURONS
Zarnadze, S.; Gloveli, T.; Dugladze, T.
Institute of Neurophysiology, Charité Universitätsmedizin Berlin

86. EFFECTS OF CD4 T CELLS DEPLETION ON VASCULAR REMODELING AND FUNCTIONAL RECOVERY IN MICE WITH EXPERIMENTAL STROKE
Zhang, T.; Odilo Engel, O.; Winek, K.; Meisel, C.; Meisel, A.; Dirnagl, U.
Department of Experimental Neurology, Charité Universitätsmedizin Berlin

Abstracts of Lectures

BETWEEN MICROSECOND PRECISION AND CONTEXT DEPENDENT ADAPTATION - NEW INSIGHTS INTO BINAURAL PROCESSING AND ITS DYNAMICS

Benedikt Grothe
Department Biology II, Ludwig-Maximilians-Universitaet Munich, Germany

The binaural circuits responsible for the initial processing of microsecond differences in the arrival times of a sound at the two ears (interaural time difference, ITD) or minute differences in the sound levels (interaural level difference, ILD) are classic examples of highly specialized neuronal structures that serve very specific functions. However, recent studies call into question the long-standing textbook scenario of hard-wired labeled-line coding principles for binaural cues as a foundation of topographic neuronal maps of auditory space. Moreover, the emerging idea of a population code of auditory space allows us to appreciate hitherto unexpected dynamics of binaural processing even at the initial sites, the medial and lateral superior olive. This, in turn, supports the notion of the context-dependent nature of spatial representations.

MOTIVATIONAL VALUE IN THE HUMAN BRAIN

Ray J. Dolan
University College London, Institute of Neurology, London, UK

Motivated behavior is strongly linked to the idea that we are disposed to act to harvest reward in our environment. Indeed, the idea that humans will expend more effort (show greater motivation) to gain a larger reward is core to operant concepts of motivation. However, acting is costly and in order to optimize behavior it is necessary to represent these action costs as well as the expected benefits from acting. In this regard how we conceptualise motivated behavior at a neurobiological level is closely linked to more general ideas related to behavioural control, for example model based and model free control in reinforcement learning. In this lecture I will consider how distinct axes of control and motivation are represented in the human brain, the neuromodulatory influence of dopamine on motivation, how motivational influences are integrated in the process of choosing and the computational processes that are enacted when learning the correct response in the face of a potential reward or punishment.

INSIGHTS INTO MECHANISMS OF STROKE AND FUNCTIONAL RECOVERY

Istvan Mody
Tony Coelho Professor of Neurology and Professor of Physiology, The David Geffen School of Medicine at UCLA, Los Angeles, CA, USA.

A large portion of the estimated $2.2 trillion stroke-related costs estimated in the U.S. between 2005 and 2050 pertains to the cost of care during the recovery period, which in turn is highly correlated with the level of disability. These figures point to the urgency of improving post-stroke neurorehabilitation, particularly since there are no drugs available, nor are there any in the pipeline, to facilitate functional recovery after stroke. Until recently, only few studies focused on the basic mechanisms and potential improvement of post-stroke functional recovery. Previous findings from our laboratory, and some promising human data about non-invasive brain stimulation in recovering stroke patients, point to an imbalance between excitatory/inhibitory cortical circuits as an obstacle in post-stroke functional recovery. Another critical question in understanding the cellular mechanisms of is related to the functioning of neural circuits during the time of ischemia. In order to gain insight into this important problem, we have developed a novel stroke model in freely moving mice and investigated the immediate and long-term effects of hippocampal artery occlusion on the activities of hippocampal cell assemblies. Understanding the acute and chronic effects of unilateral hippocampal ischemia on the activities of hippocampal neuronal ensembles will provide further strategies for preventing long-term stroke-induced disabilities.

PRION-LIKE ASPECTS OF ALZHEIMER PATHOLOGY

Mathias Jucker
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Many neurodegenerative disorders are characterized by a predictable temporal progression of specific aggregated proteins in the brain. The hallmark proteopathy is Alzheimer's disease in which multimerized and misfolded amyloid-ß peptide (Aß) is deposited in the form of parenchymal amyloid plaques and vascular amyloid. Emerging evidence suggests that ß-amyloidosis can be exogenously induced by the application of brain extracts containing aggregated Aß (Meyer-Lühmann et al., Science 2006). The amyloid-inducing agent is likely Aß itself, although in a conformation generated most effectively in the living brain. Once induced, ß-amyloid lesions spread within and among brain regions. The induced amyloid is dependent on the structural and biochemical nature of the ß-amyloid seed and of the host, an observation reminiscent of prion strains. Recently, the concept of prion-like induction, spreading, and transmission of pathogenic proteins has been expanded to include intracellular lesions such as misfolded and aggregated tau, α-synuclein and superoxide dismutase-1 (Jucker and Walker, Ann Neurol 2011). Nevertheless, the clinical implications of the transmission and propagation of misfolded proteins are not yet clear. Our latest finding that the ß-amyloid-inducing agent is partly soluble (Langer et al., J Neurosci 2011) intensifies the search for misfolded protein seeds in bodily fluids that may have diagnostic value and, potentially, be a novel target for early therapeutic intervention. Furthermore, the possibility that mechanisms exist allowing for the transport of Aß aggregates (and possibly other seeds) from the periphery to the brain (Eisele et al., Science 2010) suggests that environmental amyloidogenic seeds might act as risk factors for certain neurodegenerative diseases.

Abstracts of Welcome to Berlin Presentations

NEURAL MECHANISMS OF HUMAN COMMUNICATION

Katharina von Kriegstein

Max Planck Institute for Human Cognitive and Brain-Sciences, Stephanstr. 1A, 04103 Leipzig, Germany

In my talk I will present an overview of my group's research program that aims at identifying the sensory processes that enable us to communicate successfully with each other. We perform experiments using several methods of systems neuroscience (functional and structural magnetic resonance imaging, magnetoencephalography, and transcranial direct current stimulation) on different subject groups, i.e. healthy controls, as well as people with selective hereditary communication deficits such as face recognition deficits, dyslexia and high-functioning autism. Our two main hypotheses are that (i) specialized regions in the human brain (e.g. for voice and face processing) interact much more and at earlier stages than currently thought and that (ii) subcortical sensory structures are optimized for processing human communication stimuli. Findings of such cortical interactions and specialization at early subcortical levels are important because they may explain how the brain can achieve its speed, accuracy and robustness under adverse conditions when communicating with others.

IT'S NOT ALL LIPIDS: A PI3K INDEPENDENT ROLE FOR THE PTEN TUMOUR SUPPRESSOR AT THE CENTRAL NERVOUS SYSTEM SYNAPSE

Britta J Eickholt

Charité – Universitätsmedizin Berlin, Cluster of Excellence NeuroCure and Institute of Biochemistry, Germany

PTEN was originally identified as a tumour suppressor that functions as a central negative regulator of the PI3K signalling pathway by dephosphorylating PIP3 at the cell membrane to regulate numerous cellular functions including proliferation, growth and migration. PTEN is highly expressed in neurons and plays fundamental roles in controlling a wide range of neuronal functions. Human germline mutations in PTEN or conditional deletions of PTEN in mice have been associated with neurological disorders such as macrocephaly, ataxia, seizures, mental retardation and autism. Whilst most, if not all, of the characterised neuronal responses can be credited to PTEN's role in the regulation of membranous PIP3 and PI3K signalling, PTEN has several other potential mechanisms of action including functions independent of the lipid phosphatase activity and functions in the nucleus. The physiological significance of these PIP3-independent roles, especially in neurons, remains largely unclear.

We identified an association of PTEN with Drebrin (DBN), an actin-binding protein highly enriched in dendritic spines. Our results demonstrate that PTEN interacts directly with DBN and that this interaction negatively regulates levels a phosphorylation site present in the DBN C-terminus - serine 659 - independently of PI3K. Synaptic activity induces a transient dissociation of the PTEN-DBN complex and de-represses PTEN targeted de-phosphorylation of pS659-DBN. Our results further indicate that PTEN induced de-phosphorylation of DBN controls AMPA-mediated synaptic transmission by regulating AMPAR expression at the cell-surface. Our summarised findings provide new molecular insights into how PTEN controls synaptic efficacies by targeting the function of an actin-binding protein independent of PI3K signalling.

THE CONTRIBUTION OF EARLY-LIFE STRESS TO THE NEUROBIOLOGY OF DEPRESSION

Christine Heim, PhD

Institute of Medical Psychology, Charité University

Medicine - Berlin, Berlin, Germany

Early-life adversity, such as childhood abuse, neglect and loss, is a well-established major risk factor for developing depressive disorders later in life. This presentation will provide an overview of our human clinical research regarding the neurobiological consequences of early-life stress and their relationship to depression. Our results suggest that childhood trauma in humans is associated with sensitization of the neuroendocrine and autonomic stress response, glucocorticoid resistance, decreased oxytocin activity, immune activation, and reduced hippocampal volume, closely paralleling core features of depression. Neurobiological changes secondary to early life adversity likely reflect risk to develop depression in response to additional stresses. Changes in a connected neural circuitry implicated in emotional, neuroendocrine and autonomic control may contribute to this vulnerability. Genetic dispositions moderate the association between early-life stress and syndromal depression as well as intermediate phenotypes. This research may ultimately enable optimized clinical care, by directly targeting neurobiological pathways implicated in the link between childhood trauma and adult depression.

FAST AND SLOW INHIBITORY INTERACTIONS AMONG GABAERGIC INTERNEURONS IN HIPPOCAMPAL NETWORKS

Imre Vida

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Activity of principal neurons is governed by a small, but heterogeneous set of GABAergic inhibitory interneurons in cortical circuits. Perisomatic-inhibitory 'basket cells' (BCs) have special importance due to their precise control of the initiation and timing of action potential in target neurons. However, interneurons not only innervate principal cells, but also inhibit other interneurons. The functional relevance of these inhibitory interactions is not yet fully understood. We previously studied fast inhibition in hippocampal interneurons using a combined in vitro electrophysiological and neuroanatomical approach and found that BCs are extensively interconnected by GABAergic synapses. IPSCs mediated by ionotropic GABAA receptors at mutual inhibitory synapse had unexpectedly fast kinetics, large amplitudes and shunting effect. Properties BC-BC synapses differed from those between other interneuron types and computational analysis suggested that they are optimal for the generation of fast gamma-frequency oscillations. More recently we investigated slow GABAB receptor-mediated effects and found strong inhibition at both pre- and postsynaptic levels in BCs. The expression of GABAB, as well as the amplitude and kinetics of slow IPSCs was comparable to those in principal cells. In contrast, in several dendritic-inhibitory interneuron types GABAB receptor-mediated responses were very small or even absent. In BCs, the prominent GABAA and GABAB receptor-mediated effects could combine to produce a dynamic gamma-theta nested oscillatory pattern. In summary, our results indicate that hippocampal inhibitory interneurons are differentially regulated by multiple GABAergic mechanisms and these mechanisms may substantially contribute to the generation of the divergent activity patterns of the various interneuron types observed in in vitro, and in vivo, in the behaving animal.

Abstracts of Oral Presentations

CHARACTERIZATION OF MICROGLIA IN THE PERIVASCULAR NICHE OF GLIOBLASTOMA MULTIFORME

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Glioblastoma multiforme (GBM) is the most malignant primary brain tumor in adults. The tumor compartment contains various cell types, with about one third of microglia. In our investigations, we looked at the interaction of microglia with blood vessels and at the localisation of microglia in specific areas of the tumor to define their putative role for tumor vascularisation.
We used a syngenic tumor model of glioblastoma multiforme. Therefore, we implanted GL261 tumor cells into brains of C57/BL6 mice. Then, we evaluated brain sections for the interaction of microglia with endothelial cells and/or pericytes by immunofluorescence stainings. Furthermore, we analyzed TUNEL and Hif1α positive cells to clarify the apoptotic activity of microglia and their appearance in hypoxic areas of the tumor.
We found that up to 30% of the tumor blood vessels are associated with two or more microglia. These Iba1 positive cells are predominantly contacting endothelial cells but in the intratumoral area we detected also interaction of microglia and pericytes (approx. 15%). In addition, microglia in the hypoxic tumor area partly showed expression of Hif1α. Most of the hypoxic microglia are located in the perivascular niche or around Hif1α positive tumor cells. Surprisingly, the analyses of TUNEL staining showed only a few apoptotic cells in the tumor area. And most of these apoptotic cells were microglia which did not express Hif1α.
We discovered that microglia especially associate with endothelial cells of tumor blood vessels and express Hif1α in the perivascular niche. In future studies, the detailed investigation of the microglia and vessel interaction could lead to a better understanding of the role of microglia on tumor angiogenesis.

miR-128: A PLEIOTROPIC REGULATOR OF NEURONAL TRANSLATION

Franzoni, E; Parthasarathy, S.; Rehfeld, F.; Tarabykin, V.; Wulczyn, F. G.

microRNAs (miRNA) are a large class of non-coding RNAs important for 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 (FoxP2, Reelin), growth control (Aff4, Casc3, Phf6) and activity (Adora2a, Adora2b, RpsKa5). To better understand miR-128 roles in synaptic plasticity and cortex development we are performing in situ hybridization and gain- and loss-of-function experiments by in utero electroporation in the mouse cortex.

NOISE-INDUCED NEUROPLASTICITY IN THE CENTRAL AUDITORY SYSTEM

Moritz Gröschel[1,3], SusanneMüller[2], Romy Götze[3], Arne Ernst[1], Dietmar Basta[1,3]

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Noise exposure leads beside peripheral damage to profound changes within the central auditory system. Recent studies have shown that a noise trauma largely influences several structures involved in central auditory processing, whereby detailed pathophysiological impact still remains unclear. Further, the effects of a repeated exposure to loud noise are barely investigated. The present study should thus clarify the effects of a single or repeated noise exposure on the anatomy and physiology of central auditory structures. Normal hearing mice were exposed to a broadband noise (5-20 kHz, 115 dB) for 3 hours under anaesthesia and investigated immediately or after 7 or 14 days. Another group received a second trauma 7 days after the first one

and animals were examined one week later. Hearing thresholds were determined by auditory brainstem response recordings. Further, calcium-dependent neural activity was measured using manganese-enhanced magnetic resonance imaging. Signal strengths in several central auditory structures were analysed in all treatment groups and compared with those of normal hearing controls. In addition, cell densities were investigated in auditory brain areas to identify central neurodegeneration. The results showed a significant noise-induced hearing loss, whereby the effect of a second exposure is less compared to the first one. Calcium-dependent activity in auditory brain areas is significantly enhanced, particularly after repeated exposure. The histological findings demonstrate that noise exposure leads to a dramatic cell loss in the entire auditory pathway, even after a repeated trauma. Due to the fact that auditory thresholds do not change in a similar manner it could be hypothesized that, to some extent, calcium activation is associated with protection from hearing loss.

RESPONSES OF ADULT AND NEONATAL MICROGLIA IN VITRO TO NEUROTRANSMITTERS/HORMONES AFTER ACTIVATION WITH LPS, IFN-GAMMA AND IL-4

Pannell M, Wolf S, Matyash V and Kettenmann H

MDC, Berlin

Microglia, the immune cells of the brain, undergo a process of activation in pathology. Activation of microglia is controlled by substances such as cytokines, chemokines or growth factors. Neurotransmitters/hormones have also been identified as factors controlling microglial functions. We recently identified functional neurotransmitter/hormone receptors for endothelin, histamine, substance P and serotonin in adult murine brain slices and found distinct populations with selective responsiveness (Seifert 2011). In this study we compared the responsiveness of freshly isolated and cultured microglia from neonatal and adult mice to different neurotransmitter/hormones using Ca2+ imaging as readout. We analyzed the % of microglia responding to endothelin, histamine, substance P, serotonin, galanin, somatostatin, angiotensin II, vasopressin, neurotensin, dopamine, carbachol and nicotine. Only a small fraction (1 - 20 %) of microglial cells were responsive in all three preparations. To induce activation into a proinflammatory phenotype, we applied LPS to cultured cells for 24h. The population of endothelin-sensitive neonatal microglia increased from 6 to 47%, while in the adult, the histamine, substance P, serotonin, galanin and angiotensin II-sensitive population increased. IFN-γ as an alternate stimulus led to an increase in the number of neonatal cells responding to galanin, somatostatin, angiotensin II and carbachol. In adult cells, the histamine and carbachol response was increased. An anti-inflammatory and M2 promoting phenotype is acquired after treatment with IL-4. In adult but not neonatal cells, we observed an increase in the somatostatin sensitive population. These results indicate that microglial cells are a heterogeneous population with respect to their sensitivity to neurotransmitters/hormones and that the receptor profile changes depending on the state and mode of activation.

BREAKING THE SILENCE: A CRITICAL ROLE FOR PROSAP1/SHANK2 IN SYNAPTIC MATURATION

Stephanie Wegener, A. Vanessa Stempel, Dietmar Schmitz

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ProSAP/Shank family proteins are prominent constituents of the protein network in dendritic spines. They harbour multiple protein-protein interaction domains with which they organize the protein scaffold of the postsynaptic density (PSD). Functional studies suggest that ProSAP/Shanks serve a role in synaptogenesis and the regulation of dendritic spine morphology Mutations in the human ProSAP2/Shank3 and ProSAP1/Shank2 genes have been directly linked to autism and/or intellectual disability in humans. In a collaborative study, we have recently analyzed transgenic knockout mice lacking ProSAP1/Shank2. These mice display some core features of neurodevelopmental disorders, i.e. they are hyperactive, anxious, and impaired in their social interactions. To learn more about the function of ProSAP1/Shank2 in neuronal physiology, we characterized synaptic transmission in the hippocampus, where ProSAP1/Shank2 mice develop fewer dendritic spines. At the physiological level, they display a selective attenuation of excitatory synaptic transmission. This is accompanied by an immature signature of synaptic glutamate receptor composition and a higher fraction of silent synapses. Schaffer collateral - CA1 synapses of knockout mice were capable of undergoing long-term potentiation, however. Further studies are under way to elucidate the role of ProSAP1/Shank2 in the interplay of morphological and functional synaptic maturation.

.MODELING MITOCHONDRIAL DNA ENCEPHALOPATHIES USING HUMAN INDUCED PLURIPOTENT STEM (IPS) CELLS

Alessandro Prigione[1§], Raul Bukowiecki[1], Anne Laure Bulteau[2], Anne Lombés[2], James Adjaye1

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Defects in mitochondrial DNA (mtDNA) cause rare genetic diseases predominantly affecting neuronal cells. However, due to high clinical variability and the lack of proper animal and cellular models, the genotype/phenotype relationship remains to be elucidated.
Here, we aimed to develop novel modeling tools using neurons generated from human induced pluripotent stem (iPS) cells. These neurons will bear two unprecedented features: (i) they harbour both the nuclear and mitochondrial genome of the patients and (ii) they represent the post-mitotic cells actually affected by mtDNA disorders.
Before attempting to apply the iPS technology to mtDNA disease modeling, it was essential to fully determine the extent of mitochondrial modifications occurring within control iPS cells. Indeed, we provided the first evidence that control somatic mitochondria undergo a complex reconfiguration upon cellular reprogramming, including morphology, number, and activity (1). Moreover, we demonstrated that iPS cells obtained using retroviruses may contain mtDNA rearrangements (2).
We now take advantages of these studies to enable the application of cellular reprogramming to mtDNA disorders. Fibroblasts were obtained from three female subjects (grandmother, mother, and daughter) affected by the same mtDNA mutation of a single mitochondrial complex. iPS cells were generated using a viral-free plasmid-based method to minimize mtDNA modifications. A small molecule-based protocol for the derivation of neural progenitor cells (NPCs) (3) was applied to our control iPS cells to confirm the feasibility of this approach. NPCs generated from mtDNA-iPS cells will be then coaxed into different neuronal subtypes to unravel the intricate relationship between genotype/phenotype. The final goal is to build a cellular platform to uncover mtDNA disease-related mechanisms and to test disease-modifying agents to eventually help the diagnosis and therapy of debilitating mtDNA-related encephalopathies.

1) Prigione et al Stem Cells 2010
2) Prigione et al Stem Cells 2011
3) Li et al PNAS 2011

HEXOKINASE II-MEDIATED HYPOXIA TOLERANCE – A MOLECULAR SWITCH GOVERNING CELLULAR FATE DEPENDING ON THE METABOLIC STATE.

Philipp Mergenthaler

Experimental Neurology, Charité

The metabolic state of a cell is a key determinant in the decision to live and proliferate or to die. Hypoxia is a fundamental challenge of living organisms, interfering with homeostatic metabolism. It occurs physiologically during development or exercise and pathologically in vascular disease, tumorigenesis and inflammation. We recently demonstrated that the hypoxia-inducible factor (HIF)-1-regulated glycolytic enzyme hexokinase II (HKII) functions as a molecular switch that determines cellular fate by regulating both cytoprotection and induction of cell death based on the metabolic state of the cell. We found HIF-1-dependent upregulation of HKII in primary rat brain cortical neurons upon hypoxic stimulation. We show that overexpression of HKII potently rescues both neurons from hypoxic cell death. We further demonstrate that phosphoprotein enriched in astrocytes (PEA15) is a direct molecular interactor of HKII and show that together with PEA15, HKII inhibits apoptosis after hypoxia. In contrast, HKII accelerates cell death under glucose deprivation or in the absence of PEA15. In summary, HKII both protects from apoptosis during hypoxia and functions as a sensor of glucose availability during normoxia, inducing cell death in response to glucose depletion. Thus, HKII-mediated apoptosis may represent an evolutionarily conserved altruistic mechanism to eliminate cells during metabolic starvation to the advantage of a multicellular organism.

BRAIN ENERGY METABOLISM AND NAD(P)H FLUORESCENCE: INSIGHTS FROM MATHEMATICAL MODELLING

Nikolaus Berndt, Hermann-Georg Holzhütter

Institute of Biochemistry, Charité–Universitätsmedizin

The brain uses 20 % of whole body oxygen but accounts only for 2 % of the total body weight making it a metabolically extremely expansive organ. Switching between resting and activated state of the neuron is accompanied by large changes in the energy demand of the neuron. This entails a fast and precise regulation of the energy metabolism to ensure homeostasis of cellular ATP. To decipher the interplay between central metabolic pathways involved in the energy metabolism of a neuronal cell we developed a detailed kinetic model comprising glycolysis, the citric acid cycle, the respiratory chain, oxidative phosphorylation, the aspartate-malate shuttle and electrophysiological coupling between the cytosolic and mitochondrial compartment.

The model reproduces a variety of experimental data as, for example, release and uptake rates of lactate or consumption rates of glucose and oxygen in different activity states. In particular, the model recapitulates the characteristic time-course of NAD(P)H fluorescence observed in different activity states of hippocampal slices, comprising of an initial dip followed by a prolonged overshoot. As our generic metabolic model does not distinguish between neurons and astrocytes we conclude that this characteristic time-course of NAD(P)H fluorescence cannot be taken as a demonstration for the existence of an astrocyte-neuron lactate shuttle (ANLS).

INFLUENCE OF CLASSICAL BIOMARKERS ON COGNITIVE OUTCOME IN A CLINICAL TRIAL

Joachim LK, Fesche A, Haas B, Heuser I, Peters O

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Aim: Most clinical trials studying AChE-inhibitors in MCI have failed to influence conversion to dementia In an aborted trial testing the combination of galantamine plus memantine we have recently shown that only MCI subjects with the clinical diagnosis of presumed Alzheimers disease (AD) had a cognitive benefit after short-term treatment (Peters et al. 2011). In this sample of MCI pts, we studied the influence of CSF-biomarkers at baseline, and the duration of treatment on the clinical outcome after 24 months.

Method: In a double-blinded placebo-controlled study 237 MCI were randomized to receive a combination therapy of galantamine plus memantine, galantamine alone or placebo. Recruitment was prematurely stopped before the planned sample size had been reached. Due to the interruption of the trial only 83 patients could be reexamined after 24 months.

Results: Two years after baseline 12 out of 83 patients (14%) fulfilled the diagnostic criteria for dementia, all of whom had belonged to the subgroup of presumed AD. Converters received treatment for 630 ± 174 days over a period of 24 months (Non-converters: 211 ± 233 days). Retrospective analysis revealed that converters were characterized by a higher ADAS-cog (15.3 ± 2 vs. non-converters: 11 ± 0.5) at baseline; ADAS-cog increased significantly within 24 month only in converters. Cognitive worsening in converters was not influenced by the duration of treatment but was correlated with higher total TAU (621 ± 311 pg/ml vs. 372 ± 196 pg/ml) and lower A-beta 1-42 (508 ± 171 pg/ml vs 827 ± 391 pg/ml) at baseline.

Discussion: In an interrupted MCI-trial cognitive decline in converters was not influenced by the duration of antidementive treatment but correlated significantly with the CSF biomarker profile at baseline. We conclude that neurobiological heterogenity in MCI-trials should be strictly limited.

Poster Session I
Thursday, July 5, 2012, 15.20 - 17.30

1 LIGHT MEASUREMENT AND THE CC/EC MODEL OF NEURONAL CODING, COLOR SENSATIONS, AND JUDGMENTS

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Light entering the eye causes color sensations, which are experienced and judged by the observer as a heterogenous mixture of the six elementary color sensations (ECs) red/green, blue/yellow, black, and white [1]. The angular and spectral light intensity distributions I(λ, θ, φ), entering the eye from the respective spots (1′ x 1′) of a scene, can be measured now by a specifically composed spectral camera system. The psychophysiological CC/EC model of neuronal color coding (CC) and ECs [2] describes the relative amounts of the ECs (fatt), with r+g+b+y+bk+w=1, as steered by the neuronal CC system, according to the effectively absorbed light spectra, in relation to the respective adaptation state. The total brightness B of a color sensation is derived by the weighted sum of the specific brightness (B) of the ECs: B = rBr+gBg+bBb+yBy+wBw. In any angular elemental color sensation, only one of the ECs of an opponent EC pair (denoted by „ / „), is present at a time. Thus, only three amounts have to be judged simultanously by the observer in color analytical experiments. Color saturation S is derived e.g. as the sum of the relative amounts of the chromatic ECs: S = r+g+b+y. Hues can, e.g., be described by the ratios of the closest chromatic ECs, etc. A similarity measure (sim) of two color sensations is defined as: sim12 = [min(r1, r2) or min(g1, g2)] + [min(b1, b2) or min(y1, y2)] + min(bk1, bk2) + min(w1, w2), and realized in the related judgment (J) model of light discrimination and color sensation similarity.

[1]Hering, E., 1874. Zur Lehre vom Lichtsinne. Gerold, Wien.
[2]Backhaus, W., 2006. Psychophysiological simulations of spatial color vision. In: Fünftes Symposium „Licht und Gesundheit“, 23.-24.2.2006, TU Berlin, Tagungsband, Hauptvorträge, pp. 8-21, Hrsg. H. Kaase & F. Serick. Kistmacher, Berlin.

2 PSYCHOPHYSICAL MEASUREMENTS OF DISCRIMINATION THRESHOLDS WITH SPECTRAL LIGHT SYNTHESIZERS

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Two spectral light synthesizers have been computerized for discrimination judgments of two lights, by an observer. The synthesizers allow us to vary the intensity of each of the 1024 spectral lights (380 nm - 780 nm) by micro-mirror columns in 49152 steps. The resulting light intensity spectra project into separated halves of an Ulbricht sphere for homogeneous light mixture, finally leaving the sphere through two exit half-fields. The spectra are determined by a self-developed software that, in addition, protocols the judgments of the observer [1]. Straylight is reduced for all wavelengths, well below absolute threshold, by neutral density filters. After adaptation (closed shutter) to a steady-state, spectral visual thresholds have been determined, by turning on the stimuli for adjusting the intensity. The thresholds have been determined by the time saving up-and-down method with an individual observer (A.K.). The results show that the apparatus is best suited for further measurements with different stimulus sizes, and light adaptation states. The determined threshold intensities have been measured with a calibrated light flux measurement device (W/cm2). The data are best suited to calibrate the psychophysiological CC/EC model of photopic and mesopic color vision [2], in terms of the adaptation state and the absolute photon flux (photons/s/cm2), entering the eye.

[1] Krensel, A. & Backhaus, W., Computerized generation of photopic and mesopic light. In: Siebentes Symposium Licht und Gesundheit, 15.-16.3.2012. Eine Sondertagung der TU Berlin und der DAfP, DGP und LiTG, Hrg. S. Völker, Tagungsband, Poster Abstracts, pp. 266-270. Universitätsverlag Technische Universität, Berlin.
[2] Backhaus, W. Light measurement and the CC/EC model of neuronal coding, color sensations, and similarity judgments. (This volume).

3 TIME COURSES OF CHROMATIC ADAPTATION AND HELSON-JUDD COLOR SHIFTS

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Time courses of changes in sample and background colors, due to adaptation to monochromatic light (Helson-Judd-effect), have been measured [1]. The observer (S.B.) adapted up to six minutes to a monochromatic monitor screen (max. RGB-values), and judged the saturation C of the respective color sensations (normalized to C = 100% for t = 0 min.) in steps of Δt = 1 min.

After each judgment, two rectangular lights of lower intensities than the background, were presented for 5 s, in addition. The Helson-Judd effect becomes apparent by hue changes toward the opponent hue of the illuminant's color, categorized (0 - 2) by a discrete function H(t), according to the criteria: 1) $H(t) = 0$: no hue change visible at time t; and 2) $H(t) > 0$: a hue change occurred at time t, where $H(t) = 1$, when the color sensation color(t) differs from color($t + \Delta t$) and $H(t) = 2$, when color(t) is equal to color($t + \Delta t$).

Adaption time t	Yellow H-(t) C	Red H-(t) C	Green H-(t) C
2min	1 93%	0 87%	1 77%
2 min	1 76%	1 71%	1 60%
3 min	2 69%	1 62%	2 54%
4 min	2 62%	2 59%	2 56%
5 min	2 60%	2 56%	2 57%
6 min	2 58%	2 55%	2 54%

Tab. 1 shows exemplarily the measured time courses of H and C values for the sample of smaller intensity contrast to the background. The color of the sample of higher contrast (data not shown) remained earlier constant. The data indicate that Helson-Judd color shifts remain constant after a certain time of chromatic adaptation, well before light adaptation has completely reached a steady-state.

[1] Burmeister, S. & Backhaus, W., 2012. Psychophysiological experiments with related photopic and mesopic lights. In: Siebentes Symposium Licht und Gesundheit, 15.-16.3.2012; pp. 233-237. Universitätsverlag TU, Berlin.

4 ROLE OF MICROGLIA IN NEUROGENESIS

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Microglia are ubiquitously distributed throughout the brain, comprising approximately 10 % of all glial cells. As central nervous system (CNS)-resident immunocompetent cells, microglia play an important role in brain's innate immune defence and neuropathology, but as several recent studies have shown, microglia play a critical role in CNS homeostasis, including the generation of new neurons in the adult brain. However, the exact role of microglia in neurogenesis is not yet fully known. To investigate the impact of microglia in adult neurogenesis, the CD11b-HSVTK mouse model was used, which allows inducible, specific ablation of microglia. In the present study we demonstrate a depletion of more than 90 % of microglia cells within neurogenic regions throughout the adult brain. Following microglia depletion, neurogenesis was analysed using immunohistochemistry and quantitative RT-PCR of neurogenesis-related genes. Preliminary results reveal alterations in neurogenesis and neural stem cell maintenance in the absence of microglia cells. This study highlights the potential importance of microglia in the generation and survival of neurons in the adult brain, and further studies are underway to specifically clarify the mechanisms through which microglia impact neurogenesis.

5 SYNAPTIC TAGGING MIGHT UNDERLIE ACTIVITY-DEPENDENT FORMATION OF NEURONAL ENSEMBLES IN THE RAT HIPPOCAMPUS IN VITRO

Behrens CJ, ul Haq R and Heinemann U

Serotonin (5-HT) 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 and propagated into neocortical networks for permanent storage. Here, we used rat hippocampal slices to investigate neuromodulatory effects of 5-HT on SPW-Rs in area CA3 and CA1, which were induced within the associational commissural CA3 network by a standard long-term potentiation (LTP) protocol applied to stratum radiatum (SR) of the CA1 region. We found that 5-HT (10 or 30 μM) abruptly and reversibly suppressed SPW-Rs in a dose-dependent manner. This effect was 5-HT1A-specific, as shown by application of 8-OH-DPAT (2 μM), which mimicked 5-HT-mediated suppressive effects on SPW-Rs. This finding was corroborated by experiments where pre-application of the 5-HT1A receptor antagonist NAN-190 (10 μM) resulted in a prevention of SPW-R suppression caused by 5-HT. Furthermore, suppression of SPW-Rs by 5-HT was due to decrease in presynaptic Ca2+ uptake in axon terminals of CA3 pyramidal cells in stratum radiatum (SR) of the CA1 region as indicated by activity-dependent changes in [Ca2+]o attributed to presynaptic Ca2+ uptake following HFS (20 Hz for 10 s) applied to SR in area CA1, and paired pulse ratio of evoked EPSPs in CA1 pyramidal cells. Simultaneous intracellular recordings from CA3 pyramidal cells revealed that suppression of SPW-Rs by 5-HT was associated with a moderate hyperpolarization in all recorded CA3 neurons. In addition, we found that application of 5-HT

30 min prior to repeated stimulation prevented HFS-induction of SPW-Rs. However, when HFS was abandoned, SPW-Rs were spontaneously generated during washout of 5-HT. Since, under this condition, post-tetanic expression of SPW-Rs could be blocked by the CaMK II blocker KN-93 (20 μM), our data suggest that synaptic tagging during repeated HFS is a potential mechanism underlying the formation of functional neuronal ensembles needed for later expression of hippocampal SPW-Rs during washout of 5-HT. Previous effects of both ACh (Behrens et al., under review) and norepinephrine (NE) on hippocampal SPW-Rs in vitro (Ul Haq et al., 2011) imply synaptic tagging to be a general mechanism underlying plasticity-dependent ensemble formation during memory consolidation-related network oscillations.

6 SCAFFOLDING PROTEIN FUNTION IN THE OLFACTORY SYSTEM

Bintig

Olfactory receptors (OR) are expressed in the cilia of the olfactory sensory neurons (OSNs) in the main olfactory epithelium and are responsible for odor detection. ORs are G-protein coupled receptors (GPCR) and belong to the largest mammalian protein family (approximately 1000 genes in mice). ORs activate G□olf-protein which stimulates adenylyl cyclase-III to convert ATP into the second messenger cAMP. cAMP opens nonselective cyclic nucleotide gated cation channels, and the influx of Ca2+ and Na+ depolarizes the cell membrane and can induce action potentials in the OSNs. Furthermore, Ca2+ and cAMP can activate Ca2+ activated Cl- channels of the anoctamin family, and activate different mechanisms leading to desensitization of the signal, such as Ca2+-calmodulin or PKA. Since signalling domains in the OSNs are spatially restricted, the existence of so called olfactosomes, macromolecular complexes in the cilia of the OSNs that organize chemeosensory signal transduction components, has been proposed. We have shown previously that the multi-PDZ protein MUPP1 which is composed of 13 PDZ domains is a possible linker for the assembly of the olfactory signalling cascade. Here we show that single PDZ domains of MUPP1 interact with a broad variety of murine olfactory receptors. By co-immunoprecipitation we could furthermore hint towards the existence of an olfactory PDZome, organized via MUPP1. In in-vitro studies, MUPP1 potentiated the cAMP signalling induced by odor application. Blocking of the interaction of ORs with PDZ domains in-situ influenced signal generation and decay kinetics of the odorant response. The aim is to identify the detailed molecular composition of signalling microdomains and the mechanisms of localization of the different signalling partners, to further elucidate the factors responsible for regulating the speed and plasticity of the olfactory system.

7 FUNCTION OF CLAUDIN-3 IN BRAIN CAPILLARIES UNDER HYPO XIC CONDITIONS

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Claudin-3 (Cld3) is one of the claudins expressed at the tight junctions (TJ) in the brain. To clarify the unknown function of Cld3 in the blood-brain barrier, cerebral capillaries were isolated from wildtype (Cld3+/+) and Cld3-deficient (Cld3-/-) mice and incubated under hypoxic or normoxic conditions. Immunofluorescence analyses were done with confocal laser scanning microscopy. The TJ areas of the capillaries were identified with the junctional marker Zonula occludens protein-1 (ZO-1) and were visible in both genotypes as one or two linear patterns through the capillaries where the endothelial cells attach each other. The localization and expression of claudin-5 (Cld5) specifically tightening the blood-brain barrier was detected and checked in respect to colocalization with ZO-1. Under normoxic conditions, ZO-1 and Cld5 expression patterns were unchanged in capillaries of Cld3+/+ mice and Cld3-/- mice, which indicate that deletion of claudin-3 does not alter the general tight junction patterns in the blood-brain barrier. Under 3 h hypoxic incubations, Cld5 was considerably reduced in the capillaries of Cld3-/- mice compared to the wildtype capillaries. But, Cld5 was not internalized into the endothelial cells of Cld3-/- capillaries. Based on our data, we establish a novel function of Cld3 as a protector of Cld5 against conditions related to oxidative stress.

8 SENSITIVITY OF HYPOTHALAMIC NEURONS IN BIRDS ON DIFFERENT GLUCOSE AND LEPTIN CONCENTRATIONS

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In the bird`s brain, the primary regulatory centre for metabolism, food intake and body weight is the Nucleus infundibuli hypothalami (NI), an analogue of the mammalian Nucleus arcuatus hypothalami (NA). The major factors in the control of these processes are leptin- a circulating hormone produced by adipose tissue- and glucose. From a substantial number of papers it is known that in mammals NA-neurons are sensitive to changes in peripheral concentrations of these both substances. Additionally, in birds leptin receptors were detected in NI-neurons. So far, in birds no information on neuronal sensitivity to leptin or to glucose is available.

The aim of this work was to investigate the influence of glucose and leptin applications in different concentrations on in neuronal activity of the NI.

The experiments were carried out in brain slices (400 μm) of 19- to 23 days old domestic chickens of both sexes. Using extracellular recordings neuronal activity of NI-neurons was measured under superfusion with artificial cerebrospinal fluid combined with different glucose concentrations or acute leptin applications.
Altogether, 57 and 53 NI-neurons were investigated in terms of their sensitivity to different leptin (1, 10 and 100 nmol/l) and glucose (1 and 20 mmol/l) concentrations, respectively. It has been established that the neuronal firing rate was significantly increasing with increased leptin concentration (maximum effect at 100 nmol/l). Both tested glucose concentrations may increase or decrease neuronal activity. But successively applied in single neurons, 1 and 20 mmol/l glucose solutions induced opposite results. Finally, our investigations show mammalian like effects of leptin and glucose on NI- neurons.

9 NEURONAL BHLH PROTEINS NEX AND NDRF REGULATE CORTICAL COMMISSURE FORMATION PRIOR TO MIDLINE INTERACTIONS

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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 mutant mice, callosal neurons lack expression of the cell adhesion molecule Contactin 2 and defasciculate in the subventricular zone. Mutant axons follow random trajectories within the ipsilateral cortex instead of crossing the midline and selectively upregulate Robo1, an axonally expressed Slit receptor implicated in targeting of callosal projections. In contrast to long-range axogenesis, generation and maintenance of pyramidal neurons, initial axon outgrowth, and glutamatergic synapse assembly are grossly normal suggesting that these processes are under distinct transcriptional control. Our findings demonstrate that neocortical projection neurons require transcriptional specification by neuronal bHLH proteins to execute an intrinsic program of remote connectivity.

10 PATHWAY OF C-TERMINAL REGION OF THE CLOSTRIDIUM PERFRIN GENS ENTEROTOXIN TROUGH CLAUDIN-3 EXPRESSING CELLS

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The lysosomal storage disease Metachromatic Leukodystrophy (MLD) is a terminal illness, caused by arylsulfatase A (ASA) deficiency. An accumulation of its substrate acidic 3-O-sulfogalactosylceramide leads to a demyelination and degradation of neurons and glial cells. Patients have progressive motoric and mental disorders. Moreover, the lifespan is reduced. Enzyme replacement therapy (ERT) is a promising approach for MLD, but is limited by the blood-brain barrier (BBB). The C-terminal region of CPE (Clostridium perfringens enterotoxin; cCPE), was shown to bind a subset of tight junction proteins of the claudin protein family, like claudin-3 and -4, thereby increasing the paracellular permeability of tissue barriers. In the BBB the claudins -3, -5 and -12 are expressed. Therefore, cCPE could be used to overcome the BBB and to deliver recombinant human ASA to the brain tissue.
Our aim is to investigate cCPE-binding and -endocytosis as well as the effect of cCPE on the permeability for macromolecules of brain endothelial cell monolayers. Therefore, recombinant cCPE is used for the investigation of endocytosis in Cld3-expressing HEK-293 and Caco-2 cells by confocal microscopy and for permeability assays. In vitro cCPE opens the tight junctions for compounds up to 20 kDa. Furthermore, the expression and purification of an ASA-cCPE fusion protein as basis for ERT was established in stably transfected HEK-293 cells. Currently, we are analysing the ability of ASA-cCPE to bind and cross endothelial cells by the transcellular pathway.

11 PRO-INFLAMMATORY ENDOTOXIN ALTERS THE DYNAMICS OF MITCHONDRIAL TRANSPORT IN NEURONS.

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In multiple sclerosis (MS), it is considered that autoimmune inflammatory processes may lead to neuronal damage. Numerous studies have established a critical role for mitochondria in the pathogenesis of neurodegenerative diseases, and recent reports suggest this may also be the case for MS. Mitochondria are crucial to cell survival, not only by producing ATP, but also by functioning to maintain ion homeostasis and regulating apoptosis. Within the axon, mitochondria are delivered to, and remain in areas where metabolic demand is highest. The health of neurons depends critically on the continuous traffic, distribution and function of their mitochondria, which raises the possibility that alteration of mitochondrial dynamics could directly promote neuropathology. However, it remains poorly understood whether inflammatory stimuli can directly influence mitochondrial behavior. To address this issue, we used an ex-vivo model consisting of adult peripheral nerves explanted from the murine spinal cord, in which the axonal tracts and mitochondrial dynamics can be maintained for several hours after explantation. In this system, approximately 85% of the mitochondria were initially stationary, with a progressive decline in the fraction of motile mitochondria over time. The application of bacterial endotoxin (lipopolysaccharide, LPS), as inflammatory stimulus, induced a rapid increase in the number of motile mitochondria, selectively augmenting the proportion directed towards the cell body (retrograde transport). This effect was observed for at least 3 hours post-explantation. These results suggest an acute influence of inflammatory events on mitochondria trafficking, which may be related to changes in their membrane potential. Inflammation-induced alterations of axonal mitochondria may be implicated in neurodegeneration in inflammatory disorders of the nervous system.

12 DIRECT DIFFERENTIATION OF HUMAN IPS CELLS INTO SELF-RENEWING NEURAL PROGENITORS BY SMALL MOLECULES

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Here, we report a rapid and feasible method to derive self-renewing neural progenitor cells (NPCs) from human pluripotent stem cells. The approach adapted from Li et al.(1) gives comparable results using human embryonic stem cells (ESCs) and human induced pluripotent stem (iPS) cells generated from fibroblasts (2). The protocol exhibits major advantages in comparison to standard approaches. First, it does not require the formation of embryoid bodies (EBs). Second, it is operator-independent, as it bypasses the need for tedious manually isolating neural rosettes.
The combination of, human leukaemia inhibitory factor (hLIF), a GSK3ß inhibitor (CHIR), and a TGFß inhibitor (SB) in chemically defined media is sufficient to induce the conversion of iPS cells to highly proliferating NESTIN-positive NPCs (98 %). Inhibition of basic fibroblast growth factor (FGF) has been found important in driving neuronal conversion (3). Interestingly, FGF withdrawal coupled with the small molecule cocktail appears capable to efficiently derive NPCs. Importantly, the obtained NPC population shows distinct morphological changes within a very short time (7-10 days). NPCs could be cultured over several passages without loss of proliferation (split 1:10) as well as differentiated into TUJ1-positive neurons.
Overall, NPCs represent an inexhaustible source of neurogenic tissue exhibiting developmental potential for multiple neuronal subtypes after treatment with morphogens like retinoic acid (RA), sonic hedgehog (SHH), or FGF8. Further, the application of small molecules guaranties high reproducibility and genomic stability. Thus, after non-viral generation of iPS cells from patients, small molecule-based derivation of NPCs displays an advantageous approach to generate neurons with positional effect-free phenotypes for disease modelling.

(1) Li et al.(2011), PNAS, Vol. 108, 8299–8304
(2) Prigione et al.(2011), Stem Cells, Vol. 29, 1338–1348
(3) Greber et al.(2011), EMBO Journal, Vol. 30, 4874–4884

13 LEUKOCYTIC OPIOID RECEPTORS IN THE CONTROL OF NEUROPTHIC PAIN

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Classically, opioids (e.g. morphine) inhibit pain by acting at opioid receptors on neurons, blocking the release of excitatory neurotransmitters (e.g. glutamate and substance P). Here we examine a new concept based on the hypothesis that activation of opioid receptors on immune cells leads to the release of opioid peptides, which activate neuronal receptors, to control pain. We focus on neuropathic pain which commonly results from peripheral nerve injuries, and is refractory to conventional treatments. As a model of such condition we applied a chronic constriction injury of the sciatic nerve in mice. Immune cells infiltrating damaged nerves were isolated 2 days following the injury, and the secretion of opioid peptide Met-Enkephalin was examined using radioimmunoassay. We found that Met-enkephalin was dose-dependently released from leukocytes by selective agonists of mu-, delta- and kappa-opioid receptors. This release was abrogated by the respective opioid receptor antagonists, was absent in cells from mice lacking Met-enkephalin or opioid receptors, and was abolished by the pertussis toxin, but not by cholera toxin, indicating the involvement of Gi- (but not Gs) coupled opioid

receptors. Our results suggest that opioid peptides are secreted from immune cells following activation of opioid receptors, which might contribute to the attenuation of pain. The use of natural opioidergic pain killers and their peripheral leukocytic receptors offers a potential approach for the pain control without adverse centrally-mediated side effects (e.g. dependence and addiction).

14 TRAIL-EXPRESSING NK CELLS ARE NOT BENEFICIAL IN THE MOUSE MODEL OF MULTIPLE SCLEROSIS

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Interferon-beta (IFN-ß) is the most widely used immunomodulatory therapy in relapsing multiple sclerosis (MS). Although it reduces the risk of relapse and detains clear anti-inflammatory properties, IFN-ß mechanisms in MS are not yet fully understood due to the complex natures of both drug and disease. Moreover, a substantial group of patients fails to respond to this treatment

Thus, validating previously identified IFN-ß biomarkers in the mouse model of MS, experimental autoimmune encephalomyelitis (EAE) will help unravel its mode of action.
TRAIL (TNF-related apoptosis inducing ligand) aroused interest due to its dual function as both a death ligand and a potent immunoregulatory effector. We showed that in MS patients, increased soluble TRAIL in the periphery correlates with a stable clinical status in the case of an IFN-ß treatment. Moreover, we detected a deficient TRAIL expression on NK cells from MS patients after culturing in vitro with IFN-ß. Therefore, we hypothesised that TRAIL-production by NK cells may represent a mechanism involved in IFN-ß mediated benefit during MS.
To dissect the role of TRAIL-expressing NK cells in EAE, we performed an NK cell transfer using NK cells from the TRAIL-/- mouse, which constitutively lacks TRAIL. Surprisingly, the results contradicted our original hypothesis. Transfer of wild-type TRAIL+/+ NK cells pre-incubated with or without IFN-ß prior to EAE induction in TRAIL-/- mice induced a more severe disease course compared to controls. However, transfer of TRAIL-/- NK cells showed a protective effect, which was more pronounced when cells were not pre-incubated with IFN-ß. This suggests that IFN-ß-induced factors other than TRAIL seem to diminish the protective activity of NK cells in EAE.
In conclusion, we observed that IFN-ß-treated NK cells are not protective in EAE, and that this lack of protection is mediated by TRAIL. Nonetheless, TRAIL seems to be only partially responsible for disease worsening, and other products resulting from IFN-ß activation of NK cells are potentially operating negatively in EAE. These findings shed light on the potential risks and benefits of NK cell therapy as an MS treatment.

15 GENETIC MODELS FOR THE STUDY OF MLIN41, A STEM CELL REGULATOR OF THE MIRNA PATHWAY

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miRNAs are small, non-coding RNAs with a global influence on the proteome. They regulate fundamental physiologic processes, from early development to synaptic plasticity, stemness and pluripotency. The let-7 miRNA has emerged as a central regulator of neural stem cell differentiation and viability. We have shown that let-7 activates the miRNA pathway by inhibiting two pluripotency genes, Lin28 and Lin41. Lin41 (also known as Trim71) is an E3 ubiquitin ligase of the Trim family, that targets the RISC protein Ago2 for degradation by the proteosome, therefore downregulating global miRNA activity, and let-7 in particular, at early developmental stages. Consistent with this model, expression studies have shown a reciprocal relationship between let-7 and Lin41 in early nervous system development, and a gene trap mouse deficient in Lin41 displays embryonic lethality at E9.5 with a penetrant neural tube closure defect. To study the dynamics of Lin41 regulation of Ago2 and the miRNA pathway, and the requirement of Lin41 for early neural tube morphogenesis, we have generated embryonic stem cells from the gene trap line that are deficient in Lin41.
In the postnatal CNS, Lin41 expression is restricted to multicilated ependymal cells lining the four ventricles. However, nothing is known about miRNA regulation or Lin41 function in this lineage. We will describe initial characterization of Lin41 expression and function in whole mount ventricle preparations and in primary ependymal culture. We will report on progress toward a conditional KO mouse that will allow selective ablation of Lin41 in radial progenitors and ependymal cells.

16 FUNCTIONAL SYNAPTIC CON NECTVITY BETWEEN LAYER 2 CORTI CAL EXCITATORY AND INHIBITORY NEURONS IN VIVO

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The presynaptic spike and subsequent postsynaptic response is the fundamental unit of information processing in the brain. Remarkable progress has been made in recent years in identifying microcircuits of the neocortex and characterizing synaptic connectivity of excitatory and inhibitory neurons in vitro. Though in vitro approaches can give detailed properties of synaptic transmission and organization of local microcircuits they lack critical information concerning the functional properties of synaptically connected neurons. For example, there is little information on how synaptically connected neurons behave during sensory processing or how synaptic transmission is affected by ongoing cortical activity and changes in cortical state. Here we use two-photon targeted whole-cell recordings to investigate synaptic transmission in vivo in mouse forepaw primary somatosensory cortex. We make 2-3 simultaneous patch clamp recordings from nearby pyramidal and inhibitory interneurons in layer 2 of urethane anesthetized GAD67 mice and test for synaptic connectivity and tactile sensory responses.

17 DECREASE OF ASTROCYTIC GLUTA MATE TRANSPORTER CURRENT AND GLUTAMATE-INDUCED DEPRESSION OF SYNAPTIC GABA RELEASE IN THE STRIATUM OF MICE CARRYING A MUTANT FORM OF THE HUNTINGTIN GENE.

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Changes in glutamate uptake have been implicated in the pathogenesis of Huntington's disease (HD). In this inherited polyglutamine disorder accumulation of intracellular toxins causes a variety of deficits including synaptic dysfunction. Using a well characterized model of HD (R6/2) we addressed two questions: i) Is astrocytic glutamate transport impaired? ii) If so, what are the consequences for synaptic GABA release in the striatum, where excessive activation of glutamatergic synaptic inputs is reported to induce heterosynaptic depression of GABAergic synaptic inputs. Whole cell recordings were performed in SR101-labelled striatal astrocytes (SR+A), in addition to recording of Na-transients from SBFI-loaded SR+A. Both approaches showed a significant difference between wild-type mice (WT) and mice carrying the mutant htt (CAR). Our results suggest that impairment of astrocytic GLT-1 must be considered as a possible cause of tonic elevation of ambient glutamate which, in its turn, may lead to a tonic activation of metabotropic glutamate receptors.

To clarify the consequences of tonic mGluR activity in the striatum we tested the effects of a variety of mGluR blockers on synaptic GABA release in response to activation of single presynaptic units by minimal stimulation. The experiments identified a tonic depressant action of mGluR5 on synaptic GABA-release involving a presynaptic CB1-dependent action of endocannabinoids. This depression is enhanced in CAR mice, in line with the hypothesis that weakness of astrocytic glutamate uptake may cause a reduction of synaptic GABA release.

The characteristics of the eIPSCs further suggest that the most affected GABAergic connection is the one established on striatal GABAergic output neurons (SONs) by GABAergic interneurons (INs). The latter are known to form a potent and strongly divergent connection with soma-near compartments of the postsynaptic neuron. Since this input is inhibitory both in WT and CAR mice it may be concluded that weakness of GABAergic IN-SON transmission could be one of the mechanisms underlying impaired information processing in the striatum of HD. It will be important to find out whether this form of synaptic dysfunction precedes the neurodegeneration. If altered GABA signaling already occurs at the advent of HD it may be another important target for pharmacological intervention.

18 STROKE INDUCED IMMUNO-DEPRESSION IS MEDIATED BY PARA SYMPATHETIC ACTIVATION

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Infection is a common and severe complication after cerebral ischaemia, caused by an immunodepressive state. Whereas up to now the sympathetic nervous system and the hypothalamus-pituitary-adrenal axis are identified as mediators of stroke induced immunodepression, in this study we aimed to elucidate the role of the parasympathetic nervous system therein. The parasympathetic nervous system represents under physiological circumstances a fast feedback mechanism to limit the pro-inflammatory stimulus of the innate immune system, preventing a potentially harmful

overactivation of the immune system after infectious or inflammatory stimuli.
After experimental stroke, we observed an increased parasympathetic activity, using heart rate variability measurements via radio-telemetry. More importantly, the interruption of the "Cholinergic anti-inflammatory pathway", either by vagotomy or by using specific knock-out animals impaired in cholinergic signaling, decreased bacterial load in the lung after Middle Cerebral Artery occlusion (MCAo). Our data suggest, that parasympathetic activation after stroke inhibits both, alveolar macrophages and lung epithelium cells, thereby disabling the first line of antibacterial defense in the lung promoting life-threatening post-stroke pneumonia.

19 INVOLVEMENT OF SUBICULAR PRINCIPAL CELLS IN THE GENERATION OF NETWORK GAMMA FREQUENCY OSCILLATIONS

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The subiculum as the output structure of the hippocampal formation is capable of the generation of network activity in the theta as well as in the gamma frequency band. It is not known, however, how the two types of subicular principal cells, intrinsically bursting cells and regular spiking cells, contribute to the generation of network oscillatory activity. Extracellular field and intracellular sharp microelectrode recordings from the stratum pyramidale of the subiculum were performed from 400 μm thick mouse hippocampal slices. Kainate (400 nM) was bath applied to induce gamma frequency network oscillations. Biocytin was used for morphological identification of the recorded cells. Both principal cell types could morphologically be identified as pyramidal cells with axons leaving the subiculum. However, these cell types differ concerning their intrinsic as well as their firing properties in the active network. The intrinsically bursting cells appear to be tightly correlated to the field discharging right before and after the peak of the local field potential whereas regular spiking cells display a constant firing scheme less correlated with the field. We suggest that the two subicular principal cell classes may play different roles during the generation of gamma rhythm within the subiculum due to their different firing behavior in the active network.

20 FUNCTIONAL BRAIN REORGANIZATION FOLLOWING UNILATERAL LESIONS OF THE HIPPOCAMPAL FORMATION

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Damage to the medial temporal lobe has been shown to impair multiple memory domains. However, evidence from human patients suggests that at least some of these deficits can be significantly compensated for. We have shown previously that the corresponding functional reorganization may depend on lesion etiology and time course of the underlying disease. In particular, adult patients with shorter disease courses (benign brain tumors) showed an associative memory deficit that was not observed in patients with disease onset during childhood or adolescence (hippocampal scleroses), despite similar lesion characteristics. The mechanisms by which this occurs are largely unknown.
Here we studied patients with focal lesions to the right hippocampal formation and different preoperative disease courses (5 patients with benign brain tumors, preop. duration of epilepsy 1.8 $\pm$ 0.6 years; 6 patients with hippocampal sclerosis, preop. duration of epilepsy 14.3 $\pm$ 2.0 years) and 13 healthy controls. Subjects performed three variants of a delayed match-to-sample task while whole-brain images were acquired on a 3-T MRI scanner. Consistent with our previous results, patients with benign brain tumors showed a selective deficit for associative memory while hippocampal sclerosis performed like controls. Compared to brain tumor patients, sclerosis patients showed increased activation of left anterior hippocampus, bilateral middle frontal gyrus, bilateral frontal pole, bilateral caudate nucleus and an additional region in left lateral prefrontal cortex. A similar pattern of activation was found when sclerosis patients were compared with healthy controls. These activations were absent in brain tumor patients when compared to controls.
These results show that long-standing damage to the medial temporal lobes leads to significant reorganisation of brain networks mediating associative memory, including the the contralateral hippocampus and lateral prefrontal areas bilaterally. The data suggest that behaviourally successful compensation of lesions to the human hippocampal formation depends critically on the time course of the underlying pathology.

21 HISTONE METHYLATION IN CEREB RAL ISCHEMIA AND NEUROPRO TECTION

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Significant changes in gene expression occur in the pathology of cerebral ischemia. A panoply of both neuroprotective and deleterious genes are differentially regulated during brain injury maturation. Epigenetic mechanisms known to be involved in gene regulation seem to be crucial for both, infarct maturation and endogenous neuroprotection. Findings from our group show that manipulation of either DNA methylation or histone acetylation can induce a state that resembles endogenous tissue preservation and results in limitation of damage in case of stroke (Endres 2001, Meisel 2006). For instance, pre-treatment with histone deacetylase inhibitor Trichostatin A protects mice from ischemic brain injury (Yildirim 2008). The involvement of histone methylation in cerebral ischemia remains to be elucidated.
We explore the role of histone de-/methylating enzymes in ischemic injury and tolerance. As an in vitro model of ischemia we use oxygen-glucose deprivation (OGD). Histone methyltransferase SU(VAR)3-9 is a critical enzyme responsible for catalyzing the formation of heterochromatin, a mark of gene repression; however the role of this enzyme in transcriptional repression during stroke remains unknown. Our results demonstrate that pharmacological blockade of SU(VAR)3-9 with Chaetocin, a specific inhibitor of SU(VAR)3-9, leads to a neuroprotective effect upon OGD in rat cortical neurons. Using RNAi and overexpression experiments, we want to characterize the cerebroprotective action and targets of SU(VAR)3-9 inhibition, as this may provide a viable mechanism for manipulating transcriptional repression during cerebral ischemia.

22 SMALL MOLECULE MEDIATED CONVERSION OF TOXIC OLIGO MERS TO NON-TOXIC AMYLOID FIB RILS

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Pre-fibrillar assemblies of amyloid-ß (Aß) polypeptides such as soluble oligomers or protofibrils rather than mature, end-stage amyloid fibrils are widely held to cause neuronal dysfunction and memory impairment in Alzheimer's disease (AD). This suggests that reducing the prevalence of transient Aß intermediates by stimulation of amyloidpolymerization might decrease toxicity. Here, we report the acceleration of Aß fibrillogenesis through the action of the orcein-related small molecule O4, which directly binds to hydrophobic amino acid residues in Aß peptides and promotes the self-assembly of seeding-competent, ß-sheet-rich protofibrils and fibrils. Strikingly, O4-mediated acceleration of amyloid fibril formation efficiently decreased the concentration of small, toxic Aß oligomers in complex, heterogeneous aggregation reactions. In addition, O4 treatment suppressed inhibition of long-term potentiation by Aßoligomers in hippocampal brain slices. These results support the hypothesis that small, diffusible pre-fibrillar amyloid species rather than mature fibrillar aggregates are toxic for mammalian cells.

23 NOISE INDUCED APOPTOTIC MECHANISMS IN THE CENTRAL AUDITORY PATHWAY

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Introduction: Cochlear damage due to noise exposure is well known. Our Group described physiological and anatomical changes in different central auditory structures upon acoustic overstimulation. A significant loss of neurons in the entire auditory system has been shown previously. The aim of the present study was to investigate the underlying cell death pathways which are responsible for neuronal cell loss in the investigated structures.
Methods: Mice were noise exposed under anesthesia and investigated at different time points after the exposure. Unexposed mice served as normal hearing controls. Immunohistochemical techniques (TUNEL staining) were used to detect apoptotic cells in the ascending auditory pathway. Data were compared to normal hearing control animals.
Results: After acoustic overstimulation a significant increase of TUNEL positive cells was found as well as a significant decrease of the cell density within all investigated auditory areas. Apoptosis starts immediately post-exposure and lasts for several days.
Conclusion: Apoptosis related to pathophysiological changes induced by noise-exposure was shown in the present study. The understanding of the pathophysiological mechanisms could provide future insight into central correlates of noise-induced hearing loss.

24 DEPOLARIZATION IN ISCHAEMIA AFTER SUBARACHNOID HAEMORR GE-1: A CLINICAL STUDY ON THE INTENSIVE CARE UNIT

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DISCHARGE-1 is a multicenter diagnostic study that investigates whether spreading depolarization-induced depression of spontaneous brain electrical activity can be used to detect delayed cerebral ischemia in patients with aneurysmal subarachnoid hemorrhage. The primary outcome measure is the occurrence of new delayed infarcts as assessed by serial magnetic resonance imaging scans. Spreading depolarizations are measured electrocorticographically using subdural electrode strips. Due to the severity of the disease in focus, the study is carried out on the intensive care unit. Delayed cerebral ischemia occurs with a peak incidence around day 7 after the initial hemorrhage. In animal experiments, neuroprotectants were found to be most effective when given shortly after the onset of acute neuronal injury or when they are preadministered. Thus, delayed cerebral ischemia - our model disease for hypoxic-ischemic injury - allows us to treat patients with a neuroprotectant before the possible insult or very shortly thereafter to prove or disprove the neuroprotective concept. Neurosurgical assessment of the aneurysm allows implantation of invasive probes. This provides the unique option to monitor the whole period of ischemic stroke development, to perform early treatment stratification according to the presence or absence of prolonged spreading depolarizations, and then record the parenchymal response to the neuroprotectant. The optimal process of this study requires a coordinated cooperation of treating and observing physicians, medical personnel of the intensive care unit and other clinical departments. Bridging the gaps between these groups and coordinating the various steps of the study is an essential task of an experienced and specially trained study nurse. We here describe in detail the prerequisites and responsibilities of a study nurse during a clinical study on the intensive care unit on the example of DISCHARGE-1. The combined effort and constant communication of all professionals involved are necessary to successfully perform such a sophisticated study.

25 INTERNALISATION OF CLAUDIN-1 AND -5

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Claudins are a family of transmembranal tight junction proteins that are involved in sealing the paracellular cleft and thus regulating the transport of molecules across the blood-brain barrier (BBB). A breakdown of the BBB due to the internalisation of claudins from the plasma membrane is a symptom associated with inflammatory diseases of the nervous system. But the mechanisms of claudin internalisation are not yet fully understood.

Using fluorescence-tagged claudin-1 (CLD1) and claudin-5 (CLD5), we have found evidence of trans-endocytosis of both claudins into the neighbouring cell in CLD1- or CLD5-transfected MDCKII cells. This occurred at cell-cells contact membranes displaying homologous CLD5/CLD5 interactions as well as at membranes displaying heterologous CLD1/CLD5 interactions. Our work aims at elucidating the mechanisms behind this endocytosis using a live-cell imaging approach, in combination with markers of endocytosis and pro-inflammatory cytokines known to cause internalisation of claudins. Further steps include researching the effects of these cytokines on functional barrier properties and immunohistochemical characterisation of the internalisation pathways followed by these claudins.

26 GATING OF HIPPOCAMPAL OUTPUT BY BETA-ADRENERGIC RECEPTOR ACTIVATION

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The subiculum is the principal target of ca1 pyramidal cells and thus serves as the major relay station for the outgoing information of the hippocampus. Subicular pyramidal cells are classified as regular- and burst-spiking cells. In regular firing cells, induction of long-term potentiation (ltp) relies on the activation of postsynaptic nmda receptors. In contrast, in burst-spiking cells, ltp is induced by presynaptic nmda receptor-mediated ca2+-influx that results in the activation of the camp-pka cascade (wozny et al., 2008 a,b). Activation of beta-adrenergic receptors at ca1-subiculum synapses induces a cell-type-specific form of chemical ltp in burst-spiking but not in regular-spiking cells (wojtowicz et al., 2010).
Using a multi-channel electrode system, we simultaneously recorded field-EPSPs in acute rodent brain slices from 59 electrodes located in the subiculum, presubiculum, parasubiculum and the medial and lateral EC to assess if beta-adrenergic receptor activation changes the information transfer from the hippocampus to its parahippocampal target structures.
We demonstrate that beta-adrenergic receptor activation modulates trafficking of hippocampal output and therefore may play an important role in the facilitation of interaction between the hippocampus and distinct parahippocampal target structures.
Activation of beta-adrenergic receptors in the subiculumgates hippocampal output information to specific target regions in the parahippocampal cortex.

27 ARC/ARG3.1 COUPLES SYNAPTIC TRAFFICKING TO THE ENDOPLASMIC RETICULUM

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The immediate early gene Arc/Arg3.1 is highly and transiently expressed after neuronal activity and its mRNA is actively transported into dendrites and spines of neurons. Experiments with Arg3.1 knockout mice demonstrate that Arg3.1 is essential for the consolidation of long-term memories in a variety of behavioural paradigms. Different interaction partners of Arg3.1 have been described and suggest a role for Arg3.1 in neurodegenerative diseases like Alzheimer's Disease, potentially through regulation of endosomal sorting of disease relevant proteins. Other known interaction partners also point in the direction of vesicle endocytosis and intracellular sorting. This prompted us to further investigate the role of Arg3.1 by specifically identifying membrane bound or transmembrane interaction partners. Using Split-Ubiquitin Yeast 2 Hybrid analysis we identified two novel interaction partners, which we named TMP1 and TMP2. Both are so far uncharacterized multiple pass transmembrane proteins that can be implicated in vesicle trafficking based on sequence homology. By expression of tagged versions of TMP1 and TMP2 in different cell types we demonstrate that both proteins are localized to the endoplasmic reticulum (ER), and we show that both proteins are found in the ER of neurons including branches of the ER in distal tips of dendrites. Topology analysis reveals that the N-termini of both proteins face the cytoplasm and potentially convey the interaction with Arg3.1. Genomic analysis and semi quantitative RT-PCR establishes that TMP2 is alternatively spliced resulting in mRNAs with different 3'-UTRs but encoding identical proteins. One of these transcripts is induced by neuronal activity in cultured hippocampal neurons and in the hippocampus of mice after induced seizures. Taken together, our results identify two novel transmembrane proteins that extend the range of the trafficking function of Arc/Arg3.1 to the ER.

28 ON THE LOCATION OF THE SOMA IN INSECTS

Janina Hesse

In a typical textbook neuron, both axon and dendrites arise from the cell body. This scheme describes a common morphology of mammalian neurons. In the insect central nervous system, however, only one thin process arises from the cell body. After a couple of micrometers, dendritic trees branch from this neurite and the main process continues as the axon. In constrast to many mammalian neurons, the soma is „externalized". We hypothesize that the divergent evolution of the location of the soma between insects and mammals was fostered by evolutionary constraints. Optimal soma location may be influenced by energy efficiency of neuronal signaling and action potential propagation.

29 LONG-RANGE TEMPORAL CORRELATIONS IN THE SUBTHALAMIC NUCLEUS OF PATIENTS WITH PARKINSON'S DISEASE

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Neuronal activity in the subthalamic nucleus (STN) of untreated patients with Parkinson's disease (PD) is characterized by excessive neuronal synchronization, especially in the beta frequency range. However, less is known about the temporal dynamics of neuronal oscillations in PD. In this respect long-range temporal correlations (LRTC) are of special interest since they quantify neuronal dynamics on different time scales and were shown to be relevant for optimal information processing in the brain. While the presence of LRTC was demonstrated in cortical data, their existence in deep brain structures remains an open question. We investigated (1) whether LRTC are present in local field potentials (LFP) recorded from bilateral STN at wakeful rest in ten patients with PD after overnight withdrawal of levodopa (OFF), and (2) whether LRTC can be modulated by acute levodopa treatment (ON). In order to quantify the temporal dynamics in the amplitude fluctuations of neuronal oscillations the Detrended Fluctuation Analysis was utilized. We demonstrated for the first time the presence of LRTC in STN, extending up to 50 sec. The ON state was characterized by significantly stronger LRTC compared to the OFF state, both in beta (13–35 Hz) and high-frequency (> 200 Hz) oscillations. The existence of LRTC in subcortical STN provides further evidence for their ubiquitous nature in the brain. The weaker LRTC in the OFF state might indicate limited information processing in the dopamine-depleted basal ganglia. The present results suggest LRTC as a potential biomarker of pathological neuronal processes in PD. Supported by DFG KFO 247.

30 THE ROLE OF MICROGLIAL TLR2 IN MICROGLIA-GLIOMA INTERACTION

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Malignant gliomas are the most frequent primary tumors of the brain and these tumors have a poor clinical prognosis. Glioma tissue is infiltrated and surrounded by microglia/brain macrophages. We have recently shown that glioma induce a pro-tumorigenic phenotype of microglia. Via Toll-like receptor 2 (TLR2) signalling, glioma trigger the expression of the metalloprotease MT1-MMP in microglia which promotes tumor progression (Markovic et al., 2005, Vinnakota et al., in preparation). In search for an endogenous TLR2 ligand released from glioma cells, we screened glioma conditioned medium (GCM) by mass spectrometry for enogenous TLR2 agonists produced by glioma cells and found Versican, an extracellular matrix proteoglycan and a reported ligand of TLR2. To examine if Versican is the ligand mediating the glioma-microglia crosstalk, we silenced Versican expression in GL261 murine glioma cells. Primary microglia were then stimulated with GCM from siRNA-Versican and non-target transfected GL261 cells and microglial MT1-MMP expression was analyzed by real-time PCR. An almost 2-fold up-regulation in microglial MT1-MMP expression was observed using GCM from non-target transfectants while the expression was reduced with GCM from Versican knock-down GL261 transfectants. Our preliminary results suggest that Versican released from glioma is an important mediator to induce the pro-tumorigenic phenotype of glioma-associated microglia.

Markovic, D. S., R. Glass, et al. (2005). „Microglia stimulate the invasiveness of glioma cells by increasing the activity of metalloprotease-2." J Neuropathol Exp Neurol 64(9): 754-762.

31 PHYSIOLOGICAL ROLE OF HIGH FREQUENCY OSCILLATIONS IN THE HUMAN GLOBUS PALLIDUS INTERNUS

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High frequency oscillations (HFO) have been found in several brain areas. It has been shown that they are present in the nucleus subthalamicus in Parkinson's disease patients.
Here, we test whether HFO are also present in the globus pallidus internus (GPi), in patients with dystonia undergoing deep brain stimulation (DBS). To this end, we recorded local field potentials in 7 dystonia patients (2 females, 5 males, mean age: 53.1 ± 3.2 years), one or two days after surgical implantation of DBS electrodes, during rest with eyes open (filter: 0.5-1000 Hz, sampling rate: 5 kHz). Deep brain activity was recorded over 4 minutes from the adjacent contacts of the macroelectrode (0-1, 1-2, 2-3). We analyzed the resting power spectra (FFT size 4096, Hanning window) with 1 Hz frequency resolution. Broad individual peaks were defined as local elevations of power in which the 21 contiguous bins centred on the peak had to be significantly different ($p<0.05$) to the mean of the 10 adjacent bins below and 11 adjacent bins above. We found HFO in 13 out of 14 hemispheres (28 out of 41 recordings), while the maximum was randomly distributed along the contact pairs of the electrode. The mean peak frequency for the best contact pairs was 239.2 ± 13.6 Hz.
Here, we show for the first time that HFO are also present in the GPi in dystonia. Our findings support the hypothesis of a potential physiological role of HFO within the basal ganglia – cortical network. Its potential role in motor control will be investigated in future studies.

32 REGENERATION AFTER SPINAL CORD INJURY IN MICE WITH STEM CELL GRAFT TRANSPLANTATION

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Objective: After spinal cord injury (SCI), primary and secondary damage occur due to endogenous processes. We established a new technique with implantation of a specific directed green fluorescent protein (GFP) subventricular zone (SVZ) graft. We could easily distinguish graft from host cells, stable monitor the ingrowth of transplanted cells at the SCI site and can study their role in the regulation of endogenous regenerative processes.
Methods: For SCI in C57/bl6 mice a hemitransectomy at the Th8 level was performed. Immediately afterwards the 0,5mm3 GFP SVZ graft was implanted. Control mice received GFP motor cortex or olfactory bulb grafts. Corticospinal tracts were traced with BDA. Motor impairment and functional regeneration were measured using BMS. Mice were sacrificed after 3, 7, and 14 days. 20μm cryostat sections were analyzed for the survival of the GFP grafted cells, axonal regrowth and the size of the glial scar was counted and measured.
Results: In a majority of our studied mice the GFP graft survived the observation period. Using histological analyses we are perfectly able to distinguish host cells from implanted, firmly expressing GFP cells.

GFP expressing neurons, blood vessels and astrocytes were identified with immunocytochemistry. BMS showed a slightly better outcome of the experimental group, which was not statistically significant.
Conclusion: For the first time we present a new technique that allows monitoring the cell fate of transplanted progenitor cells derived from the SVZ over a long period, circumventing thereby the incomplete tracing techniques widely used. Our method will help to develop a new way to overcome some of the detrimental effects of SCI. By interposing the disrupted nerve fibers with a graft we are able to help regrowing axons to find their way, thus establishing reconnections and resulting in lesser motor impairment.

33 CDK5RAP2 EXPRESSION DURING MURINE AND HUMAN BRAIN DEVELOPMENT

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Primary autosomal recessive microcephaly type 3 (MCPH3) is a rare human disease characterized by a reduction of the brain volume, particularly of the cerebral cortex, and mental retardation. MCPH3 is caused by homozygous mutations in the highly conserved centrosomal protein Cycline dependent kinase 5 regulatory subunit-associated protein 2 (CDK5RAP2). The biological mechanism leading to MCPH3 is not known. Understanding the role of CDK5RAP2 during normal brain development is an important step towards revealing its pathomechanism in MCPH3. We describe the spatiotemporal expression of CDK5RAP2 during murine and human brain development. Cdk5rap2 is highly expressed during early stages of murine brain development. Immunofluorescence experiments show high Cdk5rap2 immunopositivity within the ventricular zone of the neocortex and the rhombic lip during early embryonal stages, and at later stages the immunopositivity is also detected in the subventricular zone, hippocampus and cerebellum. At postnatal day 0 (P0), Cdk5rap2 can be detected in all cortical layers with predominance in the VZ/SVZ and cortical upper layers. The immunoreactivity of Cdk5rap2 decreases as the brain matures. Co-staining experiments show that Cdk5rap2 is enriched in proliferating cells and early neurons, while most mature neurons are Cdk5rap2 negative. Cdk5rap2 colocalizes with centrosome markers and partially colocalizes to Golgi network markers. Our findings in human tissue confirm those in mouse tissues, underlining the function of CDK5RAP2 in cell proliferation and arguing for a conserved role of this protein in the development of the mammalian cerebral cortex.

34 EFFECTS OF SUDDEN UNILATERAL DEAFNESS ON BILATERAL SPIRAL GANGLION CELL DENSITY

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Recently we were able to show a contralateral hearing loss in unilateral deafened guinea pigs. This effect is possibly a result of contralateral hair cell or spiral ganglion cell loss. The aim of this study was therefore to evaluate the effect of mechanical unilateral deafening in normal hearing guinea pigs on unilateral cochlear hair cell and bilateral spiral ganglion cell density. Normally hearing guinea pigs were unilaterally deafened by the destruction of intra-cochlear structures in the first turn of the cochlea (wide cochleostomy, insertion of a filled silicon tube filling the whole diameter of the cochlea). Deafened animals and normal hearing controls were exposed to a standardized acoustic environment with a level of up to 65dB for 90 days. After this stimulation ABR measurements were performed on both groups and the cochleae were harvested for further exploration. Cochleogramms of the basilar membranes were created and hair cell counts performed for the frequencies between 400 Hz and 25 kHz. The modiolus was cut, stained and the spiral ganglion cell density was determined. Hair cell counts showed no significant loss of contralateral outer hair cells in the deafened animals compared to the controls. The evaluation of the spiral ganglion cell density showed significant effects only on the deafened side. As no outer hair cell damage on the contralateral cochlea was detected, the decreased ABR thresholds seem to be due to plastic changes in the spiral ganglion cells and possibly in the central auditory pathway. The present results show clearly the impact of interaural interaction in unilateral deafness.

35 SEMI-AUTOMATIC QUANTIFICATION OF VESSEL DIAMETER IN INTRAVITAL TIMELAPSE MICROSCOPY

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Background: Quantification of blood vessel dynamics during microscopy can aid in understanding of disease pathomechanisms e.g. in stroke or Alzheimer's disease but manual analysis is limited due to potential grader bias.
Objective: To detect and quantify vessel diameter changes in intravital timelapse microscopy minimizing grader bias.
Methods & Results: Images were acquired in anesthetized mice using two-photon imaging. A cranial window was implanted over the somatosensory cortex. The exposed cortex was double-loaded with a Ca2+ indicator and the astrocyte-specific indicator Sulforhodamine 101. To outline the vasculature, fluorescein isothiocyanate-dextran was administered intravenously. An image stack containing the vessel was created from the green channel, followed by co-registration to correct shifting artifacts. A line ROI on the first slice, which then automatically propagated through the stack, defined the vessel's cross-section. Noise reduction was performed using anisotropic diffusion, followed by a contrast limited adaptive histogram equalization to enhance the vessel structure. Seed points considered belonging to the vessel wall were automatically detected on both sides of the vessel. These points were then used to initialize a fast marching approach for the final segmentation. The results were shown as a function giving the vessel diameter at each time unit. The method was then applied and validated within a research framework in Alzheimer's disease.
Conclusion: We present a semi-automatic detection method of vessel diameter changes from timelapse microscopy. Using this approach we could quantify vessel diameter changes in a model of Alzheimer's disease strongly limiting grader bias.

36 INTRACAROTID INJECTION OF DEHYDROCHOLIC ACID (DHC) INDUCES CEREBRAL ISCHEMIA AND BLOOD BRAIN-BARRIER DISRUPTION

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Intracarotid application of DHC has been used to open the blood brain-barrier. This observation has drawn attention as a possible means for therapeutic studies of drug delivery into the central nervous system (CNS). Here we studied the effects of intracarotid application of DHC on regional cerebral blood flow (rCBF), intracortical direct current (DC) potential and extracellular potassium concentration ($[K^+]o$) in a rat cranial window preparation.
Male Wistar rats (n = 6; 250–350 g) were anaesthetized with thiopental-sodium (100mg/kg, i.p.), tracheotomised, and artificially ventilated. End-tidal CO_2 concentration was adjusted to approximately 35 mmHg. Body temperature was maintained at 38.0 °C with a heating pad. Systemic arterial pressure was monitored via the left femoral artery. Evans blue was administered via the left femoral vein to evaluate BBB opening. The right external carotid artery was cannulated in a retrograde manner for intracarotid injection of DHC. An open parietal window was implanted to place two K^+-sensitive microelectrodes and a laser-Doppler flowmetry probe. Epidural DC potential and was measured by an Ag/AgCl electrode at a closed frontal window.
Intracarotid application of DHC (17.5%, 1ml) induced an increase of rCBF to 373 ± 90 % followed by a decrease to 33 ± 16 % after 65 ± 85 s in 5 of 6 experiments. A shallow increase of the $[K^+]o$ from 3.0 to 9.8 ± 6.3 mM started simultaneously with the decrease of rCBF typical of cerebral ischemia. This was accompanied by ictal epileptic field potentials with an amplitude of -3.4 ± 2.3 mV, a spike duration of 64.8 ± 5.5 ms, and spike frequency of 1.2 ± 0.8 Hz in 5 experiments. Moreover, an increase of systemic arterial pressure accompanied the decrease of rCBF typical of a compensatory systemic hypertension. 45 ± 28 s after onset of the rCBF decrease we observed a sharp saddle-shaped negative intracortical DC shift of -20.3 ± 1.9 mV accompanied by a sharp rise of $[K^+]o$ to 49.1 ± 10.6 mM typical of cortical spreading depolarisation (CSD). The latency of this intracortical DC shift was 20 ± 20 s between the rostral and the caudal microelectrodes indicating a spread typical of CSD. The DC negativity and rise of $[K^+]o$ did not recover for an observation period of at least 60 min.
Here we show that intracarotid injection of DHC induces prolonged cerebral ischemia. Therefore, the procedure is not suitable for drug delivery into the CNS. The ischemia might be the consequence of severe damage to the cerebrovascular endothelium which will be investigated further.

37 ENDOGENOUSLY ACTIVATED P2 RECEPTORS MEDIATE MINOR MODU-LATORY EFFECTS ON EPILEPTIFORM ACTIVITY IN RAT MEDIAL ENTHORINAL CORTEX

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Pharmacoresistance constitutes a major clinical problem in the treatment of epilepsy.

Neuromodulation mediated by purinergic signalling is present in the brain and might provide new interesting pharmacological options. Here, we investigate a possible involvement of ATP-activated P2 receptors in ictogenesis. Recurrent epileptiform discharges (RED) were induced in slices from pilocarpine treated rats and age matched controls with bicuculline and elevated extracellular potassium concentration. Recordings were obtained from deep layers of the medial entorhinal cortex. Exogenous application of ATP reversibly lowered RED incidence to ~ 72 % in controls and to ~ 40 % in slices from pilocarpine treated rats. This inhibitory effect was mediated exclusively by adenosine A1 receptors. However, in control tissue specific antagonism of P2X7 receptors reduced slow flow potential to ~ 89 %, blockade of P2X4 receptors reduced duration to ~ 86 % while blocking P2Y1 receptors attenuated incidence to ~ 83 %. In slices from pilocarpine treated animals blocking P2Y1 receptors reduced slow field potential to ~ 81 %, while antagonism of P2X receptors did not have an effect. Our results are in line with previous evidence reporting an anticonvulsive function of adenosine A1 receptors which here are activated by exogenous application of ATP and its subsequent metabolization. Additionally, our results imply that endogenous ATP signaling is functional in ictogenesis since we discerned a small proconvulsive role for P2X4, P2X7 and P2Y1. Moreover, our results imply that epileptogenic processes may lead to increased adenosine susceptibility and to loss of proconvulsive P2X function while a small proconvulsive effect of P2Y1 receptors seems to be maintained.

38 IDENTIFICATION OF NOVEL NEURONAL JNK TARGETS

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We are interested in how signalling through the c-Jun N-terminal kinase (JNK) family of proteins influences the development and function of neurons. We have shown that aberrations of the brain-expressed JNK3 are linked to neurodevelopmental disorders, and JNK signalling abnormalities have been observed in mouse models for related diseases. We demonstrate here that disease-associated mutant proteins exhibit loss of classical kinase activity but are able to bind a subgroup of known JNK scaffolding proteins. This data, together with the fact JNKs exhibit high basal phosphorylation in neurons, provided the impetus to search for novel neuronal JNK binding partners.

We have combined the results from a recent computational study (in which JNK-docking sites in the human genome were predicted) with data from large scale phospho-proteomic studies designed to identify neuron-expressed phosphoproteins.
From the overlapping subset of proteins, we generated a list of top JNK candidate substrates for validation and further studies. We have demonstrated that a substantial proportion of our candidates, namely Shank3, PSD-95, SAP102, GPRIN and CRMP, are indeed JNK-interacting proteins. Moreover, combining sequence analysis and phospho-site prediction algorithms with site-directed mutagenesis and PhosTAG assays, we have been able to identify the precise site of JNK phosphorylation in several of our target proteins, and with custom phospho-specific antibodies, we are examining the effects of JNK-mediated phosphorylation on selected targets in primary neurons. We are currently focussing on disease-associated PDZ-domain scaffolding proteins of the Shank and PSD-95 families.

39 CONTROLLING NEURAL WAVE DYNAMICS BY NONLOCAL AND TIME -DELAYED FEEDBACK

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We model the propagation of traveling waves of spreading depression (cellular depolarization) in the cortex. An invasion of the healthy state by the depolarized state can be modeled by reaction-diffusion systems with one or two variables. The first variable is an activator, a lump variable, representing inward ionic currents and the extracellular potassium concentration, and the second variable is an inhibitor representing outward ionic currents. We use the FitzHugh-Nagumo equations with diffusion. The inhibitor dynamics changes on a slower time scale (time scale separation parameter epsilon is small). By adding a feedback control term, we can modulate the spatio-temporal dynamics. First, we consider the fast variable only and modulation of the front propagation speed by spatially nonlocal and time-delayed feedback control. Variation of control parameters (feedback gain, spatial or temporal control scales) slows down or speeds up the front propagation. Next, we consider fast and slow variables together and study the pulse propagation. The control planes for time-delayed and spatially nonlocal feedback control are similar in the efficiency of transient wave suppression except for large time delays. Bifurcation diagrams as function of epsilon are considered. The control can shift the domain of the regime of traveling waves to smaller or larger values of epsilon. Thus, the control in the brain may target the slowness of inhibitor

dynamics or rapidity of activator dynamics to stop spreading depression waves. Recent experimental data direct this modeling approach opening new perspective for stroke, traumatic brain injury, and migraine therapy.

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40 ALTERED SYNAPTIC PLASTICITY AND RHYTHMIC OSCILLATIONS IN THE HIPPOCAMPUS FOLLOWING VASCULAR INJURY AND BLOODBRAIN-BARRIER DYSFUNCTION

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Objectives: Recent studies have elucidated a key role for dysfunction of the blood-brain barrier (BBB) in the pathogenesis of neuronal dysfunction, epileptogenesis and delayed neurodegeneration. Following cortical lesions induced by photothrombosis with the skull intact opening of the blood brain barrier in the hippocampus was observed. We therefore tested for functional alterations.
Methods: For induction of photothrombosis the sensorimotor cortex of rats was exposed for 15 min to halogen light following i.v. injection of Rose-bengal (RB). Using Evans blue injections, we confirmed BBB dysfunction within the hippocampus from 12h to 1 week following treatment with no acute cell death. Intrahippocampal recordings were obtained using a telemetric system from 2 days prior to 1 week following RB treatment. Ex vivo electrophysiological recordings were obtained from the CA1 region of the hippocampal slice using routine procedures.
Results: Evans blue extravasation indicates BBB dysfunction which was largest 12h post-stroke. In-vivo recordings confirmed increased high frequency activity within the BBB-injured hippocampus. Ex-vivo recordings showed increased likelihood of spontaneous high frequency paroxysmal activity, lower threshold for spreading depolarization and reduced long-term potentiation.
Conclusions: Our findings suggest significant hippocampal dysfunction in the presence of peri-ischemic vascular injury which might underlie cognitive dysfunction in vascular pathologies.

This study was supported by the SFB TR3 and GRK 1123 and a Mercator professorship to Alon Friedman.

41 NEOCORTICAL DENDRITIC COMPLEXITY IS CONTROLLED DURING DEVELOPMENT BY NOMA-GAP-DEPENDENT INHIBITION OF CDC42 AND ACTIVATION OF COFILIN

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Neocortical neurons have highly branched dendritic trees that are essential for their function. Indeed, defects in dendritic arborization are associated with human neurodevelopmental disorders. The molecular mechanisms regulating dendritic arbor complexity, however, are still poorly understood.
Here, we uncover the molecular basis for the regulation of dendritic branching during cortical development. We show, that during development, dendritic branching requires postmitotic suppression of the RhoGTPase, Cdc42. By generation of genetically modified mice, we demonstrate that this is catalyzed in vivo by the novel Cdc42-GAP, NOMA-GAP. Loss of NOMA-GAP, leads to decreased neocortical volume, associated specifically with profound oversimplification of cortical dendritic arborization and hyperactivation of Cdc42. Remarkably, dendritic complexity can be restored in these animals by genetic reduction of postmitotic Cdc42 levels. Furthermore, we identify the actin regulator, cofilin, as a key regulator of dendritic complexity in vivo. Cofilin activation during late cortical development depends on NOMA-GAP expression and subsequent inhibition of Cdc42. Strikingly, in utero expression of active cofilin is sufficient to restore postnatal dendritic complexity in NOMA-GAP deficient animals.
Our findings define a novel cell intrinsic mechanism to regulate dendritic branching and thus neuronal complexity in the cerebral cortex.

42 PHARMACOLOGICAL PROPERTIES OF SPONTANEOUS SHARP WAVES IN THE MOUSE SUBICULUM

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Sharp wave ripple complexes in the hippocampus have been described in various in-vivo and in-vitro animal models and are implicated in memory consolidation. They are dependent on both glutamatergic and GABAergic synaptic transmission. However little is known about the effect of ion channel modulators. Insights on sharp wave pharmacology might help to develop new memory enhancers.
We recorded spontaneous sharp waves (SWs) in the subiculum of adult Black6/57 mice in-vitro. Extracellularly SWs presented as a negative field potential transient of 53±3 ms duration and 0.19±0.08 mV

amplitude, recurring with a rate of about 37±29/min. The SWs were always observed in CA1 and subiculum and sometimes in CA3 and propagated in direction CA3-CA1-subiculum. They were blokked by AMPAR/NMDAR antagonists (CNQX 30 μM + APV 30 μM) and the GABA-AR antagonist bicuculline (5 μM). Additionally the events were blocked by 5 μM acetylcholine and the muscarinic agonist carbachol (20 μM). This was unlikely due to M1 receptors, because the M1 agonist linopiridine (20 μM) increased incidence and amplitude of SWs. On the other hand the M3 antagonist zamifenacine (20 μM) increased the amplitude of SWs. Increase of extracellular potassium concentration to 8 mM also increased the amplitude of SWs. The persistent sodium channel blocker riluzole (30 μM) decreased the incidence of SWs and the HCN channel blocker ZD-7288 (20 μM) suppressed them completely. By contrast, the T-type Ca channel blocker Ni2+ (20-100 μM) had no effect on SWs properties.
In conclusion we suggest that H currents, inhibition and excitation underlie generation of sharp waves in the subiculum.

43 ZINC-IONS MODULATE OLIGOMERIZATION OF APP FAMILY PROTEINS

Mayer, M.; Kaden, D.; Schaefer, M.; Multhaup, G.

The amyloid precursor protein (APP) of Alzheimer disease is part of a larger protein family including the amyloid precursor like proteins APLP1 and APLP2. Results from knock-out studies suggest that these three proteins show a strong functional redundancy among each other. However, the physiological functions of the APP protein family members still remain questionable.
We studied the influence of metal-ions on the cellular localization of APP family proteins by live-cell-imaging. Interestingly, application of low micromolar concentrations of zinc ions forced APLP1-YFP and APLP2-YFP fusion proteins into protein clusters at the plasma membrane of living HEK293 cells and hippocampal neurons. Dynamic FRET measurements confirmed this effect for APLP1, APLP2 and also APP, suggesting that zinc stabilizes the oligomerization of these proteins.
Further FRET analyses with deletion mutants showed that this effect is rather mediated by novel zinc binding sites than by the zinc binding domain E1 which was earlier identified by us as a major zinc-binding site of APP. To analyze the possible contribution of the E2 domain we produced recombinant proteins containing the E2 sequence and performed zinc-binding experiments in vitro which confirmed the existence of a novel zinc-binding site in the E2 domain of APLP1. Mutations of this site led to a strong attenuation of zinc-induced oligomerization of APLP1 in living cells. In addition, biophysical analyses revealed an influence of zinc on structure and oligomerization of the E2 domains of APP, APLP1 and APLP2.
Our current focus is the functional relevance of zinc-mediated oligomerization of APP family proteins in neurons. APP family proteins were described to be present in presynaptic and postsynaptic compartments of living neurons. As free zinc ions can peak around 100 μM in hippocampal synapses, we suggest that APP family proteins may function as selective sensors of zinc signals at active synapses in the brain.

44 PHARMACOLOGICAL CHARACTERIZATION OF THE ACETYLCHOLINE BINDING SITE AT THE ALPHA4/ALPHA4 INTERFACE OF THE (ALPHA4 BETA2)2ALPHA4 NICOTINIC ACETYLCHOLINE RECEPTORS.

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The most abundant nicotinic acetylcholine receptor (nAChR) in the brain is the α4β2 receptor. Here, it contributes to cognition, mood, nociception and reward. α4β2 nAChRs have been implicated in neurodegenerative diseases, epilepsy and cause nicotine addiction.
The α4β2 nicotinic acetylcholine (nACh) receptor assembles in two alternate forms, (α4β2)2α4 and (α4β2)2α2. Being a heteromeric Cys loop ligand gated ion channels (LGIC), α4β2 receptors are activated by binding of agonist to sites located at the α4(+) β2(-) interfaces.
The two receptors display stoichiometry-specific sensitivity in response to agonist and antagonist binding. Recently a third binding site for ACh has been identified at the α4(+)/β4(-) interface of the (α4β2)2α4 receptor.
The ACh binding of this site has been proposed to account for the stoichiometry-specific agonist sensitivity of the (α4β2)2α4 receptor for ACh.
However, It is still unknown if other agonists with stoichiometry-specific effects are able to bind the α4(+)/α4(-) binding site, and how this may impacts the overall sensitivity of (α4β2)2α4 receptors to such ligands.
Using fully concatenated (α4β2)2α4 nACh receptors in conjunction with structural modelling, functional mutagenesis and, substituted cysteine accessibility method (SCAM) and stoichiometry-specific ligands, we have investigated the pharmacology of the binding site at the α4(+)/4(-) interface. Establishing whether these ligands bind the α4(+)/4(-)binding like ACh does, is a crucial step towards understanding how and why these compounds display different effects on (α4β2)2α4 and (α4β2)2β2βreceptors.

45 CHANGED BALANCE BETWEEN GLUTAMATERGIC AND GABAERGIC PHENOTYPE OF HIPPOCAMPAL MOSSY FIBERS FOLLOWING AMYGDALA KINDLING

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Hippocampal mossy fibers (MFs) end in large glutamatergic terminals (MFTs) indicated by the presence of the vesicular glutamate transporters (VGLUT) 1 and 2. During development and following overstimulation MFTs may also harbour GABAergic properties which represent a compensatory mechanism against pathological glutamatergic overexcitation. Recently we found that the dual transmitter pheno type is preserved in mature hippocampal MFTs. We wondered whether the glutamate/GABA balance in MFT is changed following repeated stimulations using the rat model of amygdala kindling and quantitative postembedding immunogold electron microscopy. For ultrastructural analyses we collected bilateral hippocampi of rats receiving either fast- or slowly progressing kindling. Following both types of kindling we observed an increase in the amount of VGLUT on synaptic vesicles in the MFTs of the ipsi- and contra-lateral hippocampus. We also found significantly increased levels of VGAT and GAD67 on both sides, while GAD65 was only increased on the contra-lateral side. Moreover we found ultrastructural changes in MFTs of kindled animals irrespective of the kindling progression. This includes an altered distribution pattern of SV limited to restricted areas of the terminal. Our findings indicate that during enhanced stimulation like the kindling paradigm the GABAergic properties increase in parallel with an increase in VGLUT concentration. The enhanced glutamate turnover may increase extracellular glutamate which stimulates the GABAergic phenotype due to the conversion of glutamate to GABA, thereby at least partially counteracting the pathological process.

Poster Presentations - Session II
Friday, July 06, 2010, 14.30 - 16.30

46 DIURNAL SORTING OF VGLUT1 BETWEEN VESICULAR AND PLASMA MEMBRANE COMPARTMENTS: IS THE VGLUT1/ENDOPHILIN INTERACTION THE KEY?

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Three structurally related vesicular transporters (VGlut1-3) are responsible for glutamate loading of synaptic vesicles (SV). Studies using VGlut1 or VGlut2 deletion mutants revealed the copy number per vesicle being crucial for synaptic efficiency (Weston et al., 2011). We previously showed, that the VGLUT amounts on SV change diurnally when analysing SV prepared at different times of the day. These variations are probably due to a diurnal switch of VGLUTs between the vesicular and the plasma membrane not shared by other SV proteins thereby representing an unique endocytic retrieval of VGLUTs.
VGlut1 but not VGlut2 interacts via a proline rich C terminal region with the SH3 domain of Endophilin, a protein involved in AP2/clathrin-dependent endocytosis.
The SH3 domain of Endophilin has also been shown to bind Dynamin and Synaptojanin, which are involved in the scission and uncoating of endocytic vesicles.
Next to Endophilin many other SH3 domain carrying proteins exist, such as Intersectin, a scaffolding protein with five SH3A-E domains which acts as primary scaffolding protein in the AP2/Clathrin mediated endocytosis (Voglmaier et al., 2006). Another SH3 domains containing protein is CIN85, which interacts with proteins, implicated in Clathrin-mediated receptor endocytosis. Interestingly, CIN85 also binds to the Endophilin SH3 domain via a proline rich sequence (Havrylov et al., 2010).
To analyze whether VGlut1 Endophilin interaction varies diurnally we analyzed wild type (WT) and Per2BRDM1 mice which lack a functional Period2 protein necessary for clock resetting.
Aside, we examined the Endophilin CIN85 interaction under a diurnal context.
Furthermore we aimed to identify additional interaction partners for VGlut1 like Intersectin, probably involved in the diurnal sorting of VGlut1 between SV and plasma membrane.

47 NEUROTRANSMITTER TRANSPORTERS – WHAT THEY LOVE AND HATE

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Neurotransmitters like GABA, glutamate, and serotonin are stored in synaptic vesicles (SV) by their respective vesicular neurotransmitter transporter (VGAT, VGLUT, VMAT). The transporters are driven by and differentially depend on an electrochemical gradient - composed of delta-pH and delta-Psi - across the vesicular membrane. For GABA and glutamate in particular, the ionic mechanisms including the maintenance of charge neutrality, osmotic balance and regulation of neurotransmitter loading, are still unclear. For example, glutamate uptake is stimulated by chloride (Cl-); the optimal concentration was found to be 4mM, although the mechanism by which Cl- is translocated causing SV acidification remains unknown. As the mechanisms for transporting the various neurotransmitters remain enigmatic, this promted us to investigate the underlying conditions with main focus on the Cl- dependence of neurotransmitter uptake.
SV were subjected to neurotransmitter uptake assay under defined ionic conditions in which delta-pH and delta-Psi were altered independently. Furthermore, the acidification and change in membrane potential of SV were investigated using acridine orange and oxonol VI assay, respectively. In addition we used knockout mice for G-proteins, ClC-3, and VGLUT1 to show the impact of these proteins on Cl- dependent glutamate uptake.
We could reproduce the known Cl- dependence of glutamate, but not GABA uptake in wild type as well as in all KO animals used. Glutamate uptake into SV immunoisolated against VGLUT1 or 2 was also Cl- dependent. Disrupting delta-pH causes massive increase of glutamate uptake at low millimolar Cl- concentrations, the absence of delta-Psi reduces glutamate uptake. In contrast to Schenck et al. 2009, we were unable to preloaded native SV with Cl-. Glutamate uptake is also effected by K+/Na+ replacement. Furthermore, in presence of glutamate disruption of delta-pH is stronger for GABA and serotonin uptake.

48 SPIKELETS IN HIPPOCAMPAL CA1 PYRAMIDAL NEURONS: ORIGIN AND FUNCTIONAL IMPLICATIONS

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Spikelets are brief spike-like depolarizations of small amplitude. Due to their all-or-none appearance, they are considered to represent full action potentials (APs) generated in an electrotonically distinct compartment. Recently, prominent spikelet activity was demonstrated in hippocampal CA1 pyramidal neurons in awake behaving animals (Epsztein et al., 2010, Science). However, the basic mechanisms underlying the generation of spikelets in these neurons are unknown.
Spikelets are studied mainly in inhibitory neurons in the context of electrotonic coupling via dendritic or somatic gap junctions. However, these so-called coupling potentials exhibit substantially slower dynamics than spikelets recorded from excitatory pyramidal neurons. In hippocampal pyramidal neurons, axo-axonic electrotonic coupling was instead suggested as a candidate mechanism for spikelet generation, although direct experimental evidence is rather scarce.
Analyzing computational models, we found that fast somatic spikelets can also be generated in a model of a single pyramidal neuron. These spikelets are shaped by axial (longitudinal) currents from a spike elicited at the axon initial segment (AIS) that fails to backpropagate to the soma. The backpropagation failure might occur under conditions of increased electrotonic distance between the soma and the AIS, as for example, during in-vivo bursting activity. Therefore, somatic spikelets generated within a single neuron might represent forward propagated APs that are not backpropagated into dendrites and thus do not influence dendritic plasticity. So this mechanism would enable pyramidal neurons in vivo to regulate dendritic plasticity. Moreover, spikelets could also save energy, since the large soma does not get (fully) activated during spikelet firing.
However, further theoretical as well as experimental work is needed to reveal the exact mechanism that regulates the firing of somatic spikelets vs. APs and to assess the role of spikelets in information processing in hippocampal CA1 pyramidal neurons.

49 IRON OXIDE MAGNETIC NANO PARTICLES REVEAL EARLY EVENTS IN CENTRAL NERVOUS SYSTEM INFLAMMATION.

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Inflammation of the CNS during multiple sclerosis (MS) involves disruption of the blood-brain barrier (BBB) and infiltration of peripheral immune cells,

which can be visualized using magnetic resonance imaging (MRI), both in MS patients and in the animal model experimental autoimmune encephalomyelitis (EAE). Leakage of gadolinium (Gd) contrast agents into the CNS parenchyma reveals focal BBB breakdown, which correlates with inflammatory lesions. Nevertheless, discrepencies between Gd-enhancing MRI lesions and clinical severity of MS underscores the need to develop novel MRI methods to better monitor CNS inflammation. We previously showed that very small superparamagnetic iron oxide particles (VSOP) can reveal CNS lesions in mice with established EAE, which were not detectable with Gd contrast agents. We hypothesize that these VSOP-detectable, Gd-negative lesions may reflect early inflammatory lesions. In the present study we adminstered VSOP to mice with EAE both at peak disease, and prior to onset of clinical signs. Histological examination of the inflammed CNS at peak disease showed VSOP in lesions in multiple locations in the CNS. The VSOP were especially prominent in the choroid plexus, which could also be seen by MRI. Interestingly, we observed VSOP in choroid plexus in the absence of overt inflammation in immunized mice prior to disease onset, but not in non-immunized controls. We also observed VSOP in CNS lesions with a perivascular accumulation of immune cells and an apparently intact glia limitans. Such perivascular lesions may represent a relatively early stage in the development of mature lesions with parenchymal infiltration and Gd contrast leakage. VSOP was seen both as discrete puncta associated with phagocytes, and in a diffuse form, suggesting that VSOP may enter the CNS via multiple mechanisms. Thus VSOP has potential to provide insight into early events of CNS inflammatory disease.

50 MODELING OF THE THETA RHYTHM PATTERNS IN SEPTO-HIPPOCAMPAL AREA

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Theta (3 - 12 Hz) and gamma (30 - 70 Hz) oscillations in rodent's hippocampal and septal areas have been thoroughly studied in vivo as well as in vitro. They occur during distinct cognitive states and are consider ed to be involved in memory processes. It has been shown that theta and gamma oscillations in hippocampus are modulated by inhibitory inputs from the septum [1-4].
The focus of this work is to study the influence of the connection between the septum and the hippocampus CA3 area on the modulation of network theta rhythm patterns. On the basis of earlier developed models [5,6], we use the Hodgkin-Huxley equations to construct a minimal septo-hippocampal circuit, consisting of three different cells. By changing the coupling strengths we analyze the effect of synaptic input on single neurons and define the parameter range at which different network oscillation patterns emerge. We investigate how the main characteristics of self-sustained oscillations such as phase shift and frequency change at the switching between different rhythms.
We could show that the minimal circuit exhibits rhythmic patterns whithin the theta band which are modulated by the strength of the inhibitory inputs on the CA3 interneuron.

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51 VISUALIZING MIGRATING MONO CYTES WITH VERY SMALL SUPERPA RAMAGNETIC IRON OXIDE PARTIC LES AFTER ENTORHINAL CORTEX LESION WITH MRI

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The absence of classical lymph vessels within brain tissue complicates immune surveillance of the CNS but it has been shown that immune cells can cross the blood brain barrier to reside in perivascular spaces under physiological conditions. Notably, the invasion of blood-derived monocytes to a central lesion site plays a crucial role after CNS injuries. With new very small superparamagnetic iron oxide particles (VSOP) we wanted to establish a method to monitor the invasion of blood-derived monocytes after entorhinal cortex lesion (ECL) and their migration out of the CNS into peripheral lymph nodes with magnetic resonance imaging (MRI). Two different VSOP were analyzed for their potential to label monocytes without compromising their immunobiological characteristics evaluated via FlowCytomix, immunocytochemistry and colloid phantoms. Hence, blood-derived monocytes were isolated from green fluorescent protein (GFP) expressing mice, incubated with VSOP and injected in C57Bl/6J mice directly after ECL. By means of photometric quantification of the amount of iron labelled onto monocytes we could determine the binding kinetics for VSPO within a time span of 48h. Additionally, the change of cellular cytokine secretion could be analyzed using FlowCytomix. We are aiming at monitoring the migration of

VSOP labeled monocytes using MRI and we have started to immunocytochemically analyze whole head/neck sections as well as isolated brains, lymph nodes and spleen. The evaluated VSOP showed only slight influence on immunobiological characteristics. Furthermore, with our established protocol we are now able to monitor VSOP labelled blood-derived GFP-monocytes in vivo within the CNS. Our long-term aim is to influence immunity and regeneration in the CNS by specific application of genetically-modified microglial progenitor cells and their monitoring via MRI.

52 THE β (+)/α(-) INTERFACES OF (α4β2)2α4 NICOTINIC RECEPTORS CONTRIBUTE TO RECEPTOR FUNC TION.

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The α4β2 nicotinic acetylcholine receptor (nAChR) is the most abundant nAChR in the brain. Here it modulates the release of a wide range of neurotransmitters, with implications in cognition, mood and addiction.
The α4β2 nACh receptor belongs to the Cys loop family of ligand gated ion channels. It assembles as a pentameric structure of one of two stoichiometries, (α4β2)2α4 and (α4β2)2β2. These receptors respond to ACh with low and high sensitivity respectively. The ACh binding sites are housed at the α(+)/β(-) interfaces in the N-terminal region of the protein, which is extracellular. The (α4β2)2□4 receptor has been recently shown to house an additional functional ACh binding site at the stoichiometry-specific α(+)/α(+) interface. The remaining interfaces, the β+/α- interfaces, are thought to bind allosteric modulators and/or contribute to the overall function of the receptor. Using fully concatenated (α4β2)2α4 nACh receptors in conjunction with functional mutagenesis and substituted cystine accesibility methods (SCAM) we have examined whether the β(+)/α(-) interfaces are implicated in receptor activity. Our results suggest that ligands bind at the β(+)/α(-) interface of the (α4β2)2α4 nACh receptors, with the occupancy of these non-canonical binding sites contributing to receptor function.

53 mLIN41 REGULATES THE MIRNA PATHWAY

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Mouse Lin41 is a TRIM-NHL domain protein specifically expressed in stem cell niches of the embryonic and adult brain. The TRIM-NHL proteins comprise a novel class of E3 ubiquitin ligases defined by the presence of a tripartite motif (TRIM) coupled to a NHL domain. The absence of mLin41 in mice leads to embryonic lethality and stunting together with a failure in neural tube closure (Maller Schulman, 2008). Recent work revealed an emerging role of Trim-NHL proteins in the regulation of miRNA biogenesis and function (Wulczyn, 2010). mLin41 was shown to repress miRNA-mediated translational control by inducing degradative polyubiquitination of the major miRISC component Ago2. Reciprocal regulation of mLin41 and the let-7 miRNA is a critical and novel circuit controlling self-renewal, commitment and terminal differentiation of stem cells (Rybak, 2009).
E3 ligases frequently target more than one protein in the same pathway, we therefore concentrated on the identification of further interaction partners and ubiquitination targets for mLin41 within the miRNA pathway. We show that mLin41 colocalizes and physically interacts with the Ago2 associated miRISC component Mov10 in a RNA-dependent manner. The binding site of Mov10 on mLin41 was mapped to the NHL domain. Unlike Ago2, the in vivo ubiquitination assay revealed high constitutive Mov10 ubiquitination that was decreased in the presence of the E3 ubiquitin ligase mLin41.
Activity dependent inactivation of a functional miRISC through proteasomal degradation of Mov10 was recently demonstrated to release translationally suppressed synaptic mRNAs (Banerjee, 2009). The challenge for further investigations will be to decipher the biological function of the association of the E3 ubiquitin ligase Lin41 and Mov10 and to integrate the knowledge of mLin41 and the miRNA pathway regulation both in the maintenance of pluripotency and in early neural development.

54 AMPLITUDE DYNAMICS IN CORTI COSPINAL INTERACTIONS

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Corticomuscular interactions are investigated mostly with coherence between EEG and EMG recordings, which however is not informative about local dynamics of interacting cortical and spinal neuronal populations. Here, we investigated the amplitude dynamics of sensorimotor EEG beta oscillations during an isometric task and their relation to corticomuscular coherence (CMC). The amplitude-envelopes of beta oscillations, obtained from multichannel EEG and EMG recordings, were used as a measure of local cortical and spinal-cord

synchronization. Upon an imperative stimulus, amplitude of cortical beta oscillations showed an initial attenuation, which correlated with the CMC strength. Our results also indicated that this correlation relates to the magnitude of pre-stimulus relative spectral power, which itself is correlated with both CMC and the attenuation of beta oscillations, rendering these two measures spuriously correlated. Therefore, a correlation of relative beta power with CMC provides a plausible explanation for a previously unaccounted variability of the CMC strength across subjects. Critically, we demonstrated that the amplitude-envelopes of beta oscillations in EEG and EMG are correlated on short and long time scales. Thus, the amplitude of ongoing cortical beta oscillations might directly contribute to the rhythmic spiking output of both corticospinal neurons and their motoneural spinal targets. We conclude that EEG beta oscillations, originating from the sensorimotor cortex, can transmit not only their phase but also amplitude dynamics through the spinal motoneurons down to peripheral effectors.

55 SPATIAL PROFILE ANALYSIS DETECTS EARLY RETINAL GANGLION CELL LAYER REDUCTION IN PATIENTS WITH CLINICALLY ISOLATED SYN - DROME

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Background: Clinical isolated syndrome (CIS) is considered to be one of the earliest stages of multiple sclerosis. Current reports do not support a significant impact on the retinal nerve fiber layer or the macular volume in CIS patients.
Objective: To characterize early changes in CIS patients' eyes in the retinal nerve fiber layer (RNFL) and ganglion cell layer (GCL) using a novel spatial profile analysis (SPA).
Methods: Patients with CIS and age and gender matched healthy controls underwent clinical examination and spectral domain optical coherence tomography, including peripapillary ring scans and macular volume scans to determine RNFL thickness and total macular volume (TMV). Additionally, we developed and applied a novel method termed SPA, incorporating all spatial information in combination with multiple generalized estimation equation (GEE) models and corrected with False Discovery Rate (FDR) for multiple comparisons.
Results: 40 patients and 40 age and gender matched healthy controls were included. Eyes of CIS patients with a previous history of optical neuritis (ON) showed a significant reduction in RNFL thickness and TMV compared to healthy controls. The areas of significant RNFL and GCL reductions were revealed using SPA. For CIS eyes not affected by a previous ON no significant changes in RNFL thickness were found while the TMV was significantly reduced. Importantly, in SPA, eyes without history of optic neuritis did show regions of significant GCL reduction, which were similar in spatial distribution to ON-affected eyes.
Conclusion: Reduction of macular retinal ganglion cell layer both in eyes with history and without history of optic neuritis point towards early neuronal damage in CIS and MS independent of acute demyelinating events.

56 RESPONSES OF ADULT AND NEONATAL MICROGLIA IN VITRO TO NEUROTRANSMITTERS/HORMONES AFTER ACTIVATION WITH LPS, IFN-GAMMA AND IL-4

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Microglia, the immune cells of the brain, undergo a process of activation in pathology. Activation of microglia is controlled by substances such as cytokines, chemokines or growth factors. Neurotransmitters/hormones have also been identified as factors controlling microglial functions. We recently identified functional neurotransmitter/hormone receptors for endothelin, histamine, substance P and serotonin in adult murine brain slices and found distinct populations with selective responsiveness (Seifert 2011). In this study we compared the responsiveness of freshly isolated and cultured microglia from neonatal and adult mice to different neurotransmitter/hormones using Ca2+ imaging as readout. We analyzed the % of microglia responding to endothelin, histamine, substance P, serotonin, galanin, somatostatin, angiotensin II, vasopressin, neurotensin, dopamine, carbachol and nicotine. Only a small fraction (1 - 20 %) of microglial cells were responsive in all three preparations. To induce activation into a pro-inflammatory phenotype, we applied LPS to cultured cells for 24h. The population of endothelin-sensitive neonatal microglia increased from 6 to 47%, while in the adult, the histamine, substance P, serotonin, galanin and angiotensin II-sensitive population increased. IFN-γ as an alternate stimulus led to an increase in the number of neonatal cells responding to galanin, somatostatin, angiotensin II and carbachol. In adult cells, the number responding to histamine was increased. An anti-inflammatory and

treatment with IL-4. In adult but not neonatal cells, we observed an increase in the somatostatin sensitive population. These results indicate that microglial cells are a heterogeneous population with respect to their sensitivity to neurotransmitters/hormones and that the receptor profile changes depending on the state and mode of activation.

57 ROLE OF FEEDBACK SIGNALING DURING NEOCORTICAL DEVELOPMENT

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Comprised of functionally distinct neurons, the mammalian neocortex develops from progenitors lining the dorsal aspects of the lateral ventricles. The fate and position of these neurons is decided by the time they leave the germinal zone. However, little is known about how cortical progenitors learn how many neurons of each type to produce and when to make the switch from producing one neuronal type to the next. One source of instructions to the progenitors comes from the cortical plate itself, creating a feedback loop. However, the molecular identity and mechanism of action of these cortical feedback signals is also poorly understood. Recently our lab identified Sip1 as a master regulator controlling the timing of corticogeneis. Comparing the gene expression patterns of Sip1 mutant and control cortex yielded several candidates that could play a role in feedback signaling during corticogenesis. Here, we present recent data from our lab on some of these candidates and their role in deciding cell fate switch of cortical progenitors.

58 SYNAPTIC PATTERNS IN THE STRIA TUM OF NORMAL AND R6/2 MICE, A MODEL OF HUNTINGTON'S DISEASE

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The Tg(HD-Exon1) mouse (R6/2) is an established model of the juvenile form of Huntington's disease (HD). The symptoms develop about 30 days after birth and are mostly lethal between 80 and 120 days. In human HD, symptomatic stages are characterized by a substantial reduction of striatal volume. In R6/2 mice, however, striatal neurodegeneration is reported to be mild, presumably because animals die before neuron and synapse loss can reach a degree characteristic of appropriately cared patients. Recent electrophysiological experiments on R6/2 mice in our lab have revealed a tonic mGluR-CB1-mediated depression of synaptic GABA release onto striatal output neurons (see Dvorzhak & Grantyn, this meeting) along with a reduction of tonic chloride currents via extrasynaptic GABA(A) receptors (see Wojtowicz et al, this meeting). Here we address the question whether alterations in the function of GABA in the striatum were accompanied by changes in the structural pattern of GABAergic and glutamatergic synaptic terminals. Of particular interest would be changes in the balance of these two types of synaptic afferents. Hemizygotic R6/2 males (B6CBATG(HDexon)62Gpb) were mated with C57Bl/6xCBA females and housed in an enriched environment. At weaning, all mice were given identity marks and tail-tip samples were taken for DNA extraction and genotyping by transgene PCR and determination of CAG length. Experiments were performed at the age of 70 to 85 days postnatally, when R6/2 mice carrying the transgene (CAR) had sensorimotor disturbances. For instance, the feed-clasping posture test was 100% positive. After transcardial perfusion and fixation in 4% paraformaldehyde, 20 μm sagittal sections were prepared and incubated with antibodies against MAP2, synaptophysin, vGluT and vGAT. Alexa-488, -555 and -647-conjugated secondary antibodies were applied for visualization in triple-stained preparations. A standard set of view-fields was acquired from the dorsal and ventral striatum using a 100x Zeiss objective and confocal optics. Immunostaining was quantified by means of an image analysis program developed by C. Henneberger (Nemo 1.423). We shall present results from 3 wild type and 3 heterozygote R6/2 mice. Alterations in the density or distribution of synaptic terminals in the dorsal vs. ventral striatum are defined according to the following parameters: i) number of vGAT+/Syp+ terminals per soma perimeter unit length, ii) number of vGluT+/Syp+ and vGAT+/Syp+ terminals per view field (100x100 μm) and iii) ratio of vGluT+/vGAT+ Syp+ terminals (E/I ratio). The data will illuminate the possible link between functional and structural aspects of HD-induced synaptic reorganization in the striatum.

59 THE INFLUENCE OF FILTERING ON THE EXTRACTION OF WHITE MATTER FIBER BUNDLES FROM DIFFUSION TENSOR IMAGING DATA

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Diffusion imaging is currently the only noninvasive technique allowing the estimation of white matter structure. Diffusion imaging is inherently a method generating data with low signal-to-noise ratio. Thus, filtering for image quality improvement is an important, though often neglected preprocessing step and can influence the tractography results significantly. The influence of two filters, the non-local means filter (NL-means) and the Perona-Malik filter (PM), was investigated. Both are adaptive imaging filters that were recommended for the preprocessing of Diffusion Tensor Imaging (DTI) data [1, 2]. The filters were tested on four DTI scans, conducted with isotropic voxel-size of 2mm, b-value of 1000s/mm^2, 15 b=0 images and 64 diffusion directions. The filters were applied after correction of head movement and eddy current induced distortions. Accordingly rotated gradient directions were used for tensor estimation and deterministic tractography. The results were demonstrated on well-known anatomical fiber bundles, in particular the cortico-spinal tract (CST), and cingulum bundles (CNG). For CST, the NL-means filter resulted in 45%-191% more fibers of a length above 100mm. For the PM filter the results were correspondingly between 7% and 35%. In one dataset, false positive fibers occurred that connected CST and corpus callosum. Further investigation of filter-parameters is necessary to avoid this effect. The influence of the filters on the CNG-fibers was marginal. These findings show that appropriate filters should be selected in dependence of the particular problem. Finally the determination of suitable parameter-sets is recommended for the reconstruction of different structures of the brain.

1 Wiest-Daesslé et al., MICCAI 2008, pp. 171-179, 2008
2 Parker et al., Journal of Magnetic Resonance Imaging 11:702-710, 2000

60 INDUCING CORTICAL OUT-GROWTH: A NEW IN VITRO TECHNIQUE TO STUDY NEURONAL REGENERATION IN MOTOR CORTEX – SPINAL CORD COCULTURES

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During the last year we have established a new coculture method combining murine motor cortical and spinal slices. Presently, we are analysing the influence of potentially enhancing compounds (e.g. NT-3, C3bot, CSA) on neuronal reestablishment in our experimental setup. Spinal cord (sc) was dissected from postnatal C57Bl/6 mice (P1 – P3) and chopped in a coronal plane. Motor cortex (mc) was extracted from coeval Bl/6.GFP offspring and cut along the sagittal longitudinal axis. Afterwards, the medial cortex zone was orientated to the rostral end of the mc and cocultured with agent added medium up to three weeks. Using nonfluorescent sc donors and constantly GFP-expressing cortex givers, ingrowing cortical neurons were easily distinguishable from spinal wildtype tissue. To evaluate neuronal recovery green-fluorescent fibers were counted and compared in length via confocal microscopy, selecting defined quadrants in different magnifications within the sc. Our data shows significant beneficial effects of Neurotrophine 3 and C3bot on cortical regeneration and could exclude CSA from enhancing neuronal recovery. Additionally, we detected decreased migration of green-fluorescent cortical microglia and neuronal precursor cells into spinal tissue after compound treatment. In addition, immunhistochemical staining suggests a reestablishment of cortical fibers and their connections. Thus, this method offers possibilities to test axon-regenerative properties of determined compounds as well as treatments and provides an important tool to answer a variety of questions in the field of neuronal regeneration.

61 DIFFERENTIAL PROCESSING OF SENSORY INPUT BY NEIGHBOU RING LAYER 2 PYRAMIDAL NEURONS IN WHISKER BARREL CORTEX RE VEALED BY IMMEDIATE-EARLY-GENE EXPRESSION.

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Neocortical neurons display considerable heterogeneity in spontaneous and sensory evoked firing rates, with overall firing rates being especially low in more superficial layers of the cortex. The underlying circuitry and synaptic mechanisms that leads to firing heterogeneity has not been determined. Recently, we used expression of the activity-dependent immediate-early gene c-fos to identify a more active subnetwork of layer 2 pyramidal neurons in whisker primary somatosensory cortex using a fosGFP transgenic mouse. Here we investigate the spontaneous activity and sensory response properties of fosGFP+ve and fosGFP-ve layer 2 pyramidal neurons using in vivo dual two-photon targeted whole-cell recordings in the urethane anaesthetized mouse. We show that fosGFP+ve neurons receive larger amplitude depolarising synaptic input as compared to neighboring (<100μm) fosGFP-ve neurons both during spontaneous upstates and airpuff triggered sensory responses. Surprisingly, trial-by-trial analysis of the subthreshold sensory response shows that fosGFP+ve neurons also respond with a significantly shorter latency. Examples of short-latency responding layer 2 pyramidal neurons with higher spontaneous firing rates have also been observed in dual and triple two-photon targeted whole cell recordings in wild type mice. Thus, a subpopulation of more active layer 2 neurons expresses the immediate early gene c-fos and is selectively targeted by short-latency sensory inputs.

62 ANALYSIS OF PROTEIN-PROTEIN INTERACTIONS USING SPLITEYFP PROBES: FOCUS ON PSD-ASSOCIATED PROTEINS

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Membrane-associated guanylate kinases (MAGUKs), which include the well-known PSD-95 family proteins, are arguably the most abundant scaffolding proteins at the post synaptic density of excitatory synapses. MAGUKs have multiple conserved domains involved in protein-protein interactions. In particular, MAGUKs harbor one or more PDZ domains, which are critical for binding to the C-terminal tails of numerous membrane receptors (NMDAR subunits directly, and AMPARs via the auxiliary TARPs), as well as various other cytosolic and membrane-associated synaptic proteins. Via these and other interactions, PDZ proteins serve a critical role in the assembly and disassembly of protein complexes that is required for normal synaptic transmission and proper transduction of downstream signaling events. We are interested in how these PDZ domain mediated protein-protein interactions can be modulated, and we have established a cell-based assay that enables us to explore this. The assay is based on on Bimolecular Fluorescence Complementation (BiFC), and it takes advantage of binding between synaptic proteins that are known to interact through a C-terminus–PDZ domain interaction: two non-fluorescent fragments of a fluorescent protein (EYFP) are fused to the C-terminal ends of the PDZ ligand, and following ectopic expression together with the full-length PDZ protein, complexes are formed. SplitEYFP halves thus come into close proximity with one another and generate an observable fluorescence signal. It has been demonstrated that genetic alterations, in PDZ proteins and/or in their associated ligands, clearly influence complex formation. Likewise, a role for post-translational modifications in this process has been established. We show here that genetic alterations affecting PDZ protein complex formation are clearly observable in our BiFC clustering assay, and we are currently using this system to explore how phosphorylation at specific sites in both PDZ proteins and their interaction partners regulate complex formation.

63 PROTEIN KINASE C MODULATES Ih – A PUTATIVE LINK BETWEEN INTERFERON SIGNALING CASCADE AND HYPERPOLARIZATION-ACTIVATED, CYCLIC NUCLEOTIDE-GATED (HCN) CHANNELS

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Excitability changes by Interferons (IFNs) are mediated via HCN channels conducting Ih. Yet the signaling pathways involved are not identified. HCN channels derive from four genes (HCN1-4). In the brain HCN1 is highly expressed in the neocortex. An in silico model of a neocortical layer 5 neuron suggest that changes in firing behavior are due to a modulation of multiple ion channel as by Protein kinase C (PKC). To directly test whether PKC modulates HCN1 channels, we performed patch clamp recordings in whole cell and cell attached mode in human embryonic kidney (HEK) 293 cells transfected with a dsRed_rHCN1 vector system. To activate PKC, we applied 1 mM PMA to the bath solution. In whole-cell recordings we observed a tendency towards Ih amplitude reduction ($P = 0.3$, $n = 4$). To conserve intracellular signaling we performed similar measurements in the cell-attached mode. Here Ih clearly was reduced from ($P = 0.015$, $n = 6$). However, PMA induced Ih changes were abolished by pre-treatment with the PKC inhibitor GF109203X ($P = 0.966$, $n = 7$), further suggesting that Ih is modulated by PKC. In summary, activation of the PKC in HCN1 transfected HEK293 cells reduces

Ih, in particular if the intracellular content remains intact. If the same holds true in neurons, this can be seen as a first hint that PKC, as a modulator of HCN1 channels, links IFN signaling to neuronal excitability changes.

64 THETA-PHASE CODING IN THE MEDIAL ENTORHINAL CORTEX

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When a rat moves, grid cells in its entorhinal cortex become active in multiple regions of the external world that form a hexagonal lattice. As the animal traverses one such 'firing field', spikes tend to occur at successively earlier theta phases of the local field potential ("phase precession"). While phase precession has been demonstrated for linear tracks and pooled data, it has remained an open question whether phase precession also occurs at the single-trial level and in two-dimensional environments. To study these issues, we re-analyze data from Hafting et al. (2009) and Sargolini et al. (2006) that were made available by E.I.Moser. For rats running on a linear track, we show that spike phases provide 80% more spatial information than spike counts, thereby improving the position estimate derived from a single neuron down to a few centimeters. To understand how spike phase variability limits the resolution, we analyze spike trains run by run. Phase precession on single runs is significantly stronger than the pooled-run data suggest. Furthermore, no correlations in the spike sequences exist across the multiple firing fields, suggesting that each field independently encodes physical space. In two-dimensional environments, a rat's path can curve, go through the center of the grid field, or swerve and miss the center completely; additionally, running speed is highly variable – in contrast to the linear track. Despite these differences, the slope and the correlation of phase precession in one and two dimensions are quite similar. Interestingly, runs that graze a grid field tangentially lead to steeper phase precession, as opposed to runs through the field center. If the run through one firing field is long and winding, however, phase precession slope is shallower than for short and straight runs. Such observations pose constraints on possible mechanisms of phase precession.

65 BLOCKING STROKE-INDUCED IMMUNODEPRESSION (SIDS) DOES NOT LEAD TO AGGRAVATED AUTOIMMUNE RESPONSE AGAINST THE CNS PROTEINS

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Stroke leads to stroke-induced immunodepression (SIDS) which renders the body susceptible for infections. Simultaneously SIDS might decrease the likelihood of developing autoreactive immune responses against the CNS antigens.
To study this hypothesis we used 2d2 transgenic mice that overexpress T cell receptors for myelin oligodendrocyte glycoprotein amino acids 35-55 (MOG35-55). Mice underwent a transient middle cerebral artery occlusion (MCAo) for 60 minutes. SIDS was suppressed by administrating propranolol (3x30 mg/kg) and RU486 (3x20 mg/kg) blocking overactivation of body's stress systems. Success of MCAo was confirmed by obtaining T2-weighted images. Development of CNS-targeted autoreactivity was evaluated by assessing CNS antigen specific T cell response as well as by functional outcome analyses assessing EAE score and Catwalk gait analysis.
We observed an early reduction of stroke volumes in animals where stress systems and SIDS were blocked ($p<0.001$). However, no differences were detected in the development of EAE-like symptoms after the blockade of SIDS. Both groups showed stroke-induced changes in paw and gait characteristics (such as print area, base of support, phase dispersions, normalized swing speed and stride length). However, no changes we present between the placebo and treated group.
Our results suggest that blockade of SIDS with combined treatment of propranolol and RU486 does not alter the development of CNS-directed autoreactive responses.

66 EFFECTS OF INTERACTIONS BETWEEN ION CHANNELS ON NEURONAL DYNAMICS

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Electrical signaling in our brain and heart relies on the opening or closing of individual stochastic units, so-called ion channels. Since Hodgkin and Huxley's model of action potential (AP) initiation, the prevailing assumption is that ion channels act independently; they change their open probability in response to a common signal such as the membrane voltage, but do not directly influence each other. However, evidence for additional interactions between channels accumulates.
Consequences of such enhancing or hindering interactions between ion channels for neuronal spiking dynamics can be expected. Nevertheless, they have so far received relatively little attention in the analysis of excitable membranes. Here, we use bifurcation analysis and stochastic simulations of an extended Morris-Lecar model to understand how cooperative and anticooperative gating between

ion channels changes basic sub- and suprathreshold voltage dynamics. The effects of channel interactions include the modification of the range of sustained firing and cell-intrinsic noise, the prolongation of AP duration, the occurrence of multistability and type-3-like firing. We hypothesize that channel interactions could be an efficient mechanism to regulate neuronal activity.

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67 ASTROCYTE-DERIVED PROTEINS IN THE CEREBROSPINAL FLUID AS BIOMARKERS FOR THE PATHOBIO LOGICAL STAGING OF ALZHEIMER´S DISEASE

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The quantitative analysis of biomarker proteins in the cerebrospinal fluid (CSF) substantiates the clinical diagnosis of AD especially in early disease stages. In late stages of AD Abeta and tau-protein levels have become static and are therefore unsuitable to reflect ongoing dynamic processes of AD-related neurodegeneration, as such as glia cell-related pathobiology. But, it is well established that amyloid plaques are associated with activated astrocytes. Thus, astrocyte-derived proteins like glial fibrillary acidic protein (GFAP) and S100B that are detectable in CSF might serve as markers of pathophysiological events especially in advanced AD. For a sample of 71 human CSF aliquots commercially available ELISA were used for the quantitative analysis of GFAP (IBL-International, Hamburg, Germany) and S100B (IBL). We included AD patients, healthy controls and disease controls. First we correlated standard biomarkers (abeta and tau-protein) and glia-derived proteins, furthermore we compared biomarker levels of controls and AD patients at different disease stages. When calculating the correlation coefficient (Spearman) we found significant correlations of classical biomarker values to GFAP and S100B concentrations in CSF. Comparing groups of patients at different disease stages, we found that for both markers, S100B and GFAP the average concentrations are highest in AD-patients with moderate dementia at presumably advanced disease stages. Astrocyte-derived proteins like GFAP and S100B can be reliably detected in CSF and might serve as markers for pathophysiological events in the course of the disease. Additional measurement of astroglial biomarkers might allow an improved pathobiological staging of AD.

68 TOUCHING THE BRAIN: MAGNETIC RESONANCE ELASTOGRAPHY IS A NOVEL TOOL TO QUANTIFY THE IMPAIRMENT OF CEREBRAL TISSUE INTEGRITY

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BACKGROUND: Palpating the brain in order to detect pathology was long time exclusive to neurosurgeons and pathologists. Recently, it became possible for radiologists and physicists, too: Magnetic Resonance Elastography (MRE) is a novel imaging technique allowing the in vivo assessment of brain parenchymal biomechanics non-invasively. The propagation of mechanically elicited shear waves is analyzed and provides objective information on the viscoelasticity of the tissue investigated. However, it is unclear which cellular or molecular conditions cause changes of biomechanics. Thus, we introduced a murine model of multiple sclerosis and correlated MRE-parameters to histopathology.
METHODS: By feeding Cuprizone (CPZ), reversible demyelination was induced in 2 groups of C57BL/6-mice. One group was returned to normal chow allowing for remyelination. These groups were compared to matched controls. T2-weighted scans and 3D-MRE were performed 3-weekly on a 7T animal scanner. Subsequent histological analyses comprised evaluation of myelination, extracellular matrix (ECM), immune cell infiltration and axonal damage.
RESULTS: Viscoelasticity increased in healthy and to a lesser extent in treated animals up to week 9, then decreased significantly in CPZ-fed mice. Demyelination and ECM-reorganization progressed constantly. Immune cell infiltration followed a different time course compared to MRE-parameters. There was no evidence of axonal damage.
CONCLUSION: Comparison of histological findings with alterations of MRE-parameters in CPZ-fed mice leads to these conclusions: i) viscoelasticity decreases with progressive demyelination and global ECM degradation; ii) the loss modulus decreases faster than the shear modulus and might be specific to demyelination; iii) biomechanical properties are not influenced by cellular inflammation; iv) all processes are reversible after remyelination.
Ongoing brain maturation causes an increase in viscoelasticity.

69 LPA1, LPA2, AND LPA4 RECEPTOR EXPRESSION DURING MOUSE BRAIN DEVELOPMENT

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Lysophosphatidic acid (LPA) is a small bioactive phospholipid that acts as an extracellular signalling molecule and is involved in numerous cellular processes, including cell proliferation, migration, differentiation and motility. LPA acts by binding and activating at least five known G-protein-coupled receptors: LPA1-5. In recent years, LPA has been shown to be an important player in both normal neuronal development and under pathological conditions in the nervous system. In this paper, we show the expression pattern of LPA receptors during mouse brain development, which we determined using quantitative real-time PCR (qRT-PCR) and immunocytochemistry. Only LPA1, LPA2 and LPA4 mRNA-transcripts were detected throughout development stages from embryonic day 16 (E16) until postnatal day 30 (P30) of hippocampus, neocortex, cerebellum and bulbus olfactorius in our experiments, while the expression of LPA3 and LPA5 genes was below detection level. In addition to our qRT-PCR results, we also analyzed the cellular protein expression of endogenous LPA1 and LPA2 receptors within postnatal brain slices and primary hippocampal neuron differentiation. Interestingly, we found that commercially available antibodies for LPA receptors are largely unspecific. Multiple specificity tests were performed to identify one anti-LPA1 and one anti-LPA2 antibody which satisfy the criteria of specificity. Unfortunately, we couldn't find an anti-LPA4 antibody useable in our analysis.

70 SYNAPTOPHYSIN – MASKING GEN DER DIFFERENCES IN NEURONAL PLASTICITY?

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Long term structural memory arises in particular from adjustments in the strength of neuronal synapses. One of the parameters of synaptic strength is the amount of neurotransmitter released. This release depends on the efficiency of exo- and endocytosis of synaptic vesicles (SVs) and especially on their neurotransmitter load. Generally SVs are equipped with a certain set of proteins of which synaptophysin (syp) makes for the largest share by mass. Counterintuitive to the immense bioenergetic investment for syp biosynthesis, phenotypic deviations turn out to be relatively mild in syp depletion mutants (syp-/-).
Here we present a comparative analysis of SV neurotransmitter loading including monoamines, glutamate and GABA from wild type and syp-/- mice. As the most interesting result we found neurotransmitter uptake in syp-/- mice to be sexually dimorphic, so far without evidence for gender dependent differences in SV parameters relevant for transmitter transport, i. e. the copy number of vesicular neurotransmitter transporters per SV. Thus variations in synaptophysin function may explain gender differences in brain function under healthy and pathological conditions.

71 THE IMPACT OF PRIOR KNOW LEDGE ON OBJECT SEARCH IN REAL-WORLD SCENES

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Humans are excellent at rapidly detecting objects in their complex natural environment. Earlier studies using synthetic search arrays showed that simple object features, like contrast or orientation, play a critical role in guiding attention in visual search. But object recognition in the real-world surrounding us is affected to a high degree by visual and semantic complexity. Real objects are generally composed of heterogeneous visual features and often have implicit semantic or functional relations to objects in their neighbourhood (e.g. a knife to a plate on the kitchen table).
In this study, we investigated whether prior knowledge about object location facilitates object detection in real scenes. Former studies regarding this matter using artificially manipulated scenes resulted in conflicting results.
We created a photo database of everyday scenes in which only the location of the object to be searched was arbitrarily manipulated. The stimulus set was controlled with respect to numerous psychophysical parameters like saliency and contrast in order to prevent a confounding with object position at the expected versus the unexpected location.
30 subjects were instructed to search for shortly presented objects in a scene presented afterwards. Every scene was shown only once and the presentation of photographs with objects at the expected and the unexpected position occurred at random. Reaction times were significantly shorter at the expected location, averaged across 30 subjects as well as across 110 scenes which demonstrates that

the effect is not the trivial consequence of extreme values of single subjects or single scenes. In summary our results demonstrate that prior relational knowledge is used to enhance object search in realistic environments.

72 FUNCTIONAL ANALYSIS OF THE SIN GLE NUCLEOTIDE POLYMORPHISMS (SNPS) IN THE CODING REGION OF THE β4 SUBUNIT OF NACHR

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Nicotine dependence is one of the leading causes of preventable death. Recently the genomic locus containing the nicotinic acetylcholine receptor (nAChR) subunits α3, β4 and α5 has been linked to smoking dependence in genome-wide association studies. Our previous work demonstrated, that the β4 subunit is rate limiting for receptor activity and overexpression of this subunit in mice leads to strong nicotine aversion. The ability of β4 to enhance nicotine-evoked currents depends on a single critical residue (S435) located within the membrane-associated stretch in the intracellular vestibule of the receptor. Sequence alignments revealed that 6 SNPs map to this region, one of them being the most common SNP associated with tobacco usage, D398N in the α5 subunit. Functional analyses of these and other SNPs mapping to the intracellular vestibule in Xenopus laevis oocytes demonstrated that single mutations in this domain can result in profound effects on nicotine-evoked currents. We aimed to determine the influence of the other single nucleotide polymorphisms in the coding region of β4 nAChR subunit to channel function in response to nicotine, as well as how this translated into nicotine-mediated behavior. Medial habenula (MHb) is one of a few discrete expression sites of α3β4 nAChR combination and has been linked to both nicotine consumption and pain modulation. Lentiviruses carrying the wild-type β4 subunit as well as the β4 rare missense variants were injected using stereotactic coordinates into MHb. Here we show, that mice overexpressing the β4T374I polymorphism in the MHb display strong aversion to nicotine in free-choice nicotine drinking test, whereas lentiviral delivery of β4D447Y subunit into MHb resulted in decreased sensitivity to mechanical and thermal nociceptive stimuli, as well as decreased response to acute inflammatory pain.

73 ROLE OF SIP1 IN ORCHESTERATING NEOCORTICAL CONNECTIVITY

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Abstract: The immense cognitive ability that the neocortex confers on higher primates, to a large extent is dependent on the appropriate development of neocortical connections. The formation of functional circuits in turn depends upon certain key developmental processes finally leading to synapse formations such as migration, axonal-outgrowth and branching, axonal path finding and dendritic arborisation. Here, we report that Sip1, a cortical postmitotic transcriptional repressor is essential for the appropriate establishment of neocortical connectivity by regulating many of the above-mentioned developmental events.
Smad-interacting-protein-1 (Sip1) is a DNA-binding transcriptional repressor that interacts with activated Smads, the transducers of TGF-□ signaling, and with the NuRD complex. It is expressed robustly within cortical postmitotic neurons.
Lack of Sip1 causes migrating neurons to stall within the deeper layers of the cortex. Sip1 mutants lack a corpus callosum and an anterior commissure. While cortico-thalamic connections are largely intact, cortico-subcerebral projections are completely missing. Deletion of Sip1 in postmitotic cortical neurons leads to an impairment in axonal branching also a decrease in the complexity of dendritic arborization. We are further studying factors acting downstream of Sip-1 that are potentially mediating these effect and together are helping in establishing neocortical connections.

74 AT BIRTH THE HYPERPOLARIZATION-ACTIVATED CYCLIC NUCLEOTIDE-GATED (HCN)1 SUBUNIT DOES NOT CONTRIBUTE TO RODENT NEOCORTICAL IH

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HCN1, the fast activating subunit, is a major contributor to Ih in the mature neocortex and it has been implicated in the maturation of the cortical plate. In line, our whole-cell measurements in

perinatal rat cortical plate somatosensory neurons, co-transfection of different subunit assemblies in HEK293 cells and in silico modeling suggested HCN1 to be involved in the Ih generation at birth (P0).
To further understand the actual role of the HCN1 subunit in perinatal neocortical development we performed biochemical analysis in developing rodent cortex accompanied by whole-cell patch-clamp recordings in upper cortical plate neurons in the region of the somatosensory cortex of P0 HCN1-/- and control HCN+/+ mice.
Perinatally HCN3 and HCN4 were prominently expressed in the cortex on both, mRNA and protein levels. HCN1 subunits were also present, but not glycosilated, putting its membrane presence into question. In HCN1-/- and control HCN+/+ mice cortices, cortical plate neurons exhibited an inward rectifying current upon hyperpolarization in 41.5 or 40 % respectively. ZD7288, a specific Ih blocker, substantially reduced the pharmacologically isolated current in both groups, demonstrating its identity as Ih. Functional ablation of the HCN1 subunit did not affect the maximal Ih amplitude or density. Major subunit-sensitive characteristics of Ih such as the half maximum activation voltage, the voltage dependence of activation and the kinetics of activation and deactivation were similar in neurons of HCN1-/- and HCN+/+ cortices.
In conclusion, our data show that, despite the fact that the HCN1 subunit is present at P0, its contribution to Ih at birth seems marginal, suggesting that in this model HCN3 and HCN4 are mainly responsible for this current at birth.

75 THE RELEVANCE OF AUTOPHAGY FOR HEXOKINASE II-MEDIATED PRO TECTION FROM CELL DEATH

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Regulation of cellular metabolism highly depends on the balance between biogenesis and degradation. Consequently, autophagy, a process which helps to preserve this balance, is an important factor for cellular homeostasis. Autophagy is a physiological mechanism that contributes to the turnover of cellular components (damaged proteins and organelles) and also plays an important role in metabolic stress adaption. Stress-mediated autophagy is activated in response to events such as deregulation of mitochondrial function or oxidative deficiencies which are common in many diseases including neurodegenerative illnesses. In this context, autophagy may preserve the survival of neurons at times of limited nutrient availability.
In response to metabolic deficiencies, expression of many genes including the hypoxia-inducible factor (HIF)-1-regulated mitochondrial glycolytic enzyme hexokinase II (HKII) is activated. HKII and its interaction partner phosphoprotein enriched in astrocytes (PEA15) mediate cytoprotection after hypoxia in neurons and in cancer cells but promote apoptosis in response to glucose deprivation, suggesting that HKII acts as a molecular switch. Cell death and autophagy are partly regulated by the same mechanisms. Thus, we here investigate whether HKII triggers a part of its effects through autophagic processes or not.
To study autophagic activity we measure the regulation of the microtubule-associated protein 1 light chain 3 (LC3), a major constituent of the autophagosome, under different conditions of deprivation (oxygen, glucose and oxygen-glucose deprivation). Furthermore we assess the impact of the HKII/PEA15 complex for autophagy regulation and analyze the role of autophagy in HKII/PEA15-mediated cell protection after hypoxia and apoptosis induction in response to glucose deprivation. In addition, we compare autophagic activity in neurons of wild type mice and PEA15 knock out mice to illuminate the role of PEA15.

76 WHOLE-CELL RECORDINGS FROM MOUSE FORELIMB MOTOR CORTEX NEURONS DURING TARGETED REACHING.

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Primary motor cortex (M1) controls voluntary movement. While a number of studies have documented extracellular recordings during motor tasks, there is very little data available on the synaptic activity underlying motor processing in M1. Here we present whole-cell recordings from forelimb primary motor cortex (fM1) in mice trained to perform a forelimb reach and touch task. To locate fM1 we performed electrical microstimulation in anaesthetised mice and, in good agreement with previous studies, found fM1 centered 0.3 mm anterior and 1.6 mm lateral to bregma. Up to 6 head-restrained mice were trained in parallel within 6-10 days to reach and touch a sensor. Pharmacological inactivation experiments with cortical microinjections of the GABA-A receptor agonist muscimol confirmed that the behaviour was dependent on fM1 activity. Whole-cell recordings from fM1 in awake, behaving mice revealed strong state-dependent changes in subthreshold activity. When mice were sitting still,

large amplitude, slow oscillations were observed in fM1 neurons. During reaching, by contrast, the membrane potential was depolarised and smaller amplitude, higher frequency events occurred. This confirms that state-dependent changes in cortical activity are present in alert, trained mice performing cortically dependent behaviour. Here we have developed an M1 dependent motor task that will allow investigations into the cellular, synaptic and network mechanisms underlying cortical motor control.

77 LARGE-SCALE NEURAL MODEL OF FUNCTIONAL CONNECTIVITY BETWEEN ANATOMICALLY UNCONNECTED AREAS OF THE HUMAN CORTEX

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Experimental studies in neuroscience have shown that low-frequency fluctuations (<0.1 Hz) of blood-oxygen-level-dependent (BOLD) fMRI signal acquired during resting state (i.e. without any external input) form so-called functional connectivity (FC) networks. It has also been shown that topologies of FC and anatomical connectivity (AC) networks closely correspond to each other. However, cortical pairs without direct anatomical connections also show coherent spontaneous BOLD fluctuations, suggesting that FC cannot be explained in terms of AC alone. Mechanisms generating resting state FC fluctuations are largely unknown and it has been contended that indirect connections, interregional distance and collective effects governed by network properties of the cortex play a significant role. In addition, some theoretical studies on large-scale brain networks demonstrated the importance of time delays in networks dynamics for the generation of resting state FC fluctuations. To address these questions we investigate a large-scale neural network model of human cortex resting state FC. Our model is based on an empirically derived resting state FC network consisting of 64 regions of interest (ROIs) (network nodes), which are chosen from all over the cortex. The ROIs are adapted from a study of functional segmentation of the brain cortex using high-model-order independent component analysis (ICA). There are 30 pairs of inter-hemispheric homologues, and 4 additional ROIs are chosen along the midline. The activity of each node is described by FitzHugh-Nagumo neurons. Network dynamics is modelled with different parameters for each node and different time delays to account for the finite signal propagation times between the nodes.

78 9F/1H MRI OF BRAIN INFLAMMATION IN EXPERIMENTAL AUTOIMMUNE ENCEPHALOMYELITIS

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Abstract: In the present study we employed an animal model of MS, the Experimental Autoimmune Encephalomyelitis (EAE) to explore the in vivo uptake of fluorine (19F) nanoparticles by inflammatory cells during encephalomyleitis. Using a 32-leg 1H/ 19F birdcage coil dedicated for mouse head imaging, we detected and quantified 19F nanoparticles (containing perfluoro-15-crown-5-ether) taken up and transported by macrophages within the cerebellum following intravenous application. The application of 19F nanoparticles for imaging immune cells in conditions such as encephalomyelitis is an emerging field that will be ideal to study the kinetics of immune cell localization during the development of inflammation.

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79 PRE-SYMPTOMATIC CEREBELLAR LESIONS AND VENTRICLE ENLARGEMENT IN AN EAE MOUSE MODEL REVEALED BY MICROSCOPIC MRI

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Abstract: Microscopic MRI affords the acquisition of highly resolved images in a reasonable scan time, thereby providing the possibility to perform in vivo longitudinal studies in animal models. In this study we have detected and tracked early structural changes in brain tissue of EAE mice prior to neurological symptoms. We were able to detect a significant enlargement of the ventricles before disease manifestation and an increase in T2 relaxation time of CSF after disease onset. Microscopic MRI and T2 maps provide the opportunity to better understand the early processes involved in the development of encephalomyelitis.

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80 CHARACTERIZING THE MITOCHONDRIAL HKII-DEPENDENT MULTIPROTEIN COMPLEX USING BIMOLECULAR FLUORESCENCE COMPLEMENTATION (BIFC) AND A PROXIMITY LIGATION ASSAY (PLA)

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We recently demonstrated that the hypoxia-inducible-factor (HIF)-1-regulated glcycolytic enzyme hexokinase II (HKII) inhibits neuronal cell death after hypoxia in the presence of its interaction partner phosphoprotein enriched in astrocytes (PEA15). While mitochondrial binding of HKII is required for the antiapoptotic effect of HKII, mutants that inactivate mitochondrial binding, as well as glucose deprivation or the absence of PEA15 accelerate apoptosis. Thus, HKII together with PEA15 acts as a sensor of glucose availability during normoxia, inducing apoptosis in response to glucose depletion.
However, our data indicate the existence of a larger HKII-dependent multiprotein complex. We therefore now present methods to confirm and further investigate other putative interactors of HKII.
Among others, the proapoptotic Bcl2-family member BCL2 interacting protein 3-like (Bnip3l) and the antiapoptotic heat shock protein tumor necrosis factor receptor-associated protein-1 (TRAP1) were determined as putative interaction partners of HKII via a split-ubiquitin membrane-based yeast two-hybrid screen accomplished in our lab. We therefore investigated whether Bnip3l or TRAP1 interact with HKII using bimolecular fluorescence complementation (BiFC) and a proximity ligation-based assay (PLA). The BiFC approach is based on the complementation of a fluorescent protein when two proteins fused to non-fluorescent fragments of that fluorescent protein interact with each other. The in situ PLA technology, which uses specific antibodies conjugated to oligonucleotides for the proximity dependent generation of a detectable fluorescent signal, allows for the exact cellular localization of protein interactions in intact cells.
The precise characterization of the HKII-dependent multiprotein complex may help to understand the connection between metabolic processes, such as glycolysis and pathways regulating cell death.

81 THE IMPACT OF FOCAL CEREBRAL ISCHAEMIA ON THE COMPOSITION OF MURINE INTESTINAL MICROBIOTA

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The intestine is inhabited by the community of commensal bacteria that contains more cells than the body. In recent years the gut microbiome and the brain-gut-microbiota communication axis have received growing attention. Interestingly, it was found that gut microflora may be involved in the pathogenesis and course of central nervous system diseases. In our studies we aim to assess the composition of the intestinal flora before and after stroke – the number one cause of adult disabilities and one of the most frequent causes of death. In our initial experiment, 12 mice were subjected to either Middle Cerebral Artery Occlusion (MCAO), a well-characterized animal model of ischaemic stroke, or to sham operation. Fecal samples from each mouse were taken one day before and 48 hours after the surgical procedure. DNA was extracted from the samples and amplified using specific bar-coded primer sets targeting V1-V3 and V6-V8 hypervariable regions of 16S rRNA. As the last step 454 pyrosequencing was performed to comprehensively characterize the microbial gut

community. We observed dramatic changes in the composition of the intestinal flora before and after surgical procedures. However, the differences between MCAO and sham animals were only moderate. Our results indicate a strong influence of stress on the microbiota community. Changes in the gut flora after stroke and their possible role demand further investigations, and a functional role of microbiome changes for stroke outcome needs to be established.

82 IMPAIRED NEUROVASCULAR COUPLING TO ICTAL EPILEPTIC ACTIVITY AND SPREADING DEPOLARIZATION IN A PATIENT WITH SUBARACHNOID HEMORRHAGE

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Spreading depolarization describes a sustained neuronal and astroglial depolarization with abrupt ion translocation between intraneuronal and extracellular space leading to an abrupt cytotoxic edema and silencing of spontaneous activity. Spreading depolarizations occur abundantly in acutely injured human brain and are assumed to facilitate neuronal death through toxic effects, increased metabolic demand and inverse neurovascular coupling. Inverse coupling describes severe hypoperfusion in response to spreading depolarization. Ictal epileptic events are less frequent than spreading depolarizations in acutely injured human brain but may also contribute to lesion progression through increased metabolic demand. Whether occur with ictal epileptic events is unknown. We here describe a patient with aneurismal subarachnoid hemorrhage in whom spreading depolarizations and ictal epileptic events were measured using subdural opto-electrodes for direct current-electrocorticography and regional cerebral blood flow recordings with laser-Doppler flowmetry. Simultaneously, changes in tissue partial pressure of oxygen were recorded with an intraparenchymal oxygen sensor. Isolated spreading depolarizations and clusters of recurrent spreading depolarizations with persistent depression of spontaneous activity were recorded over several days followed by a status epilepticus. Both spreading depolarizations and ictal epileptic events where accompanied by hyperemic blood flow responses at one optode but mildly hypoemic blood flow responses at another. Of note, quantitative analysis of Gadolinium-diethylene-triamine-pentaacetic-enhanced magnetic resonance imaging detected impaired blood-brain barrier integrity in the region where the optode had recorded the mildly hypoemic flow responses. The data suggest that abnormal flow responses to spreading depolarizations and ictal epileptic events, respectively, may be associated with blood-brain barrier dysfunction.

83 REDUCTION OF TONIC ACTIONS OF AMBIENT GABA IN THE STRIATUM: DATA FROM AN ESTABLISHED (R6/2) AND A VERY RECENT (Q175) MODEL OF HUNTINGTON'S DISEASE (HD)

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The Tg(HD-Exon1) mouse (R6/2) is an established model of the juvenile form of Huntington's disease (HD). The respective heterozygotes (HETs) are viable and carry a mutant form of the human huntingtin. HD symptoms develop about 30 days after birth and are mostly lethal between 80 and 120 days of age. In the z_Q75_KI mouse (Q175, Cerebricon Ltd.) the mutation is inserted in the murine huntingtin gene. Thus, the expression of multiple CAG repeats can occur in a more appropriate genomic and protein environment. Q175 homozygote (HOM) mice develop a late onset form of HD. Both mouse models were studied at symptomatic stages, i.e. at 8-12 weeks (R6/2 HETs) and 36-52 weeks (Q175 HOMs). Average CAG length was 120±0.2 in R6/2 (range 114-127, n=137) and 184±1.1 in Q175 (range 172-195, n=29).
Two types of tonic GABA actions can be observed in normal adult striatal output neurons (SONs): i) a G-protein-mediated inhibition of synaptic GABA

release via presynaptic GABA(B) receptors and ii) a chloride current via somato-dendritic extrasynaptic GABA(A) receptors. As application of exogenous GABA reduces the frequency of spontaneous AP-dependent synaptic currents, the polarity of ambient GABA actions on the striatal output activity would be opposite in i) and ii), being inhibitory in case of ii).
It was found that both types of tonic GABA actions were reduced in mice carrying the mutant huntingtin (CAR). This conclusion is based on the following experiments. For analysis of i), unitary evoked IPSCs (eIPSCs) were elicited by striatal minimal stimulation in sagittal brain slices using whole cell patch clamp recordings. The amount of tonic presynaptic depression was quantified based on the changes induced by the GABA(B) R antagonist CGP (1 μM) in the amplitudes and paired pulse ratios of eIPSCs. For analysis of ii), whole cell holding currents were recorded in the presence of NMDA- and AMPA-antagonists, with or without additional block of mGluRs, GABA(B) Rs and action potential generation. The size of the tonic extrasynaptic chloride current was quantified on the basis of the current steps induced by application of the GABA(A) antagonist bicuculline methiodide, BMI (20 μM).
The depressant action at extrasynaptic GABA(A) R-mediated currents could be simulated by application of exogenous GABA at a concentration of 5-10 μM and was strongly potentiated in the presence of the GABA(A)R delta subunit-specific hyperagonist THIP.
Our observations suggest that alterations in the level of ambient GABA concentration may play a role in the pathogenesis of HD. A weakness of extrasynaptic tonic chloride conductance would increase the excitability of SONs and may enhance their vulnerability in HD.

84 MOLECULAR MECHANISMS OF NEUROD2/6 FUNCTIONS IN NEOCORTICAL DEVELOPMENT

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Basic helix-loop-helix (bHLH) transcription factors regulate many biological differentiation processes ranging from cell determination to complex organ development. Neurod2 (NDRF) and Neurod6 (NEX) are closely related neuronal bHLH proteins expressed in pyramidal neurons following similar spatial and temporal patterns. Disruption of either one gene in mice does not impair pyramidal neuron development. In Neurod2/6 double mutant mice, however, the Neocortex shows abnormalities in pyramidal neuron migration, layer identity, cellular proliferation and axon guidance. Using in-situ-hybridization, we recently identified misexpression of several well known genes involved in regulating those processes. We currently employ loss- or gain–of-function experiments in-vivo to investigate the involved molecular mechanisms and to identify further downstream targets.

85 DYNAMICAL SWITCHING BETWEEN HIPPOCAMPAL NETWORK STATES: ROLE OF INTERNEURONS

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The hippocampal network is capable of exhibiting in vivo and in vitro network oscillations at different frequency range: theta, gamma and sharp wave associated ripples (SWRs). However,
It is still unknown how the same neuronal circuit in the hippocampus exhibit different oscillations and dynamically switch between them. We recorded from perisomatic-targeting fast spiking basket cells and pyramidal cells in area CA3 during two different network states – spontaneously occurring SWRs and pharmacologically (kainic acid) induced gamma frequency oscillations. At the beginning the cells were recorded in cell-attached configuration and the discharge pattern and their phase relationship to simultaneously recorded local field potential was studied. The excitatory and inhibitory postsynaptic currents were analysed in whole-cell mode. Our results show that most of the pyramidal cells are silent during SWRs and discharge with a low frequency (2-5 Hz) during gamma oscillations. In contrast, all recorded fast spiking basket cells fire with one or several spikes per SWR-episode and discharge on every gamma cycle strongly phase-locked to the field oscillations. We conclude that the firing pattern/frequency of these interneurons may determine the network states in hippocampal area CA3.

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86 EFFECTS OF CD4 T CELLS DEPLETI ON ON VASCULAR REMODELING AND FUNCTIONAL RECOVERY IN MICE WITH EXPERIMENTAL STROKE

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Stroke is a multiphasic process involving intense inflammatory responses. However, the complex role of inflammation as well as immunity in infarct maturation is largely unknown. Experimental studies on the role of infiltrating lymphocytes in damage and repair after cerebral ischemia imply the involvement of adaptive immunity. In our 60min middle cerebral artery occlusion (MCAo) model, we detected delayed and dominant infiltration of CD4+ T cells in the ipsilateral hemisphere, which started from day 7 and achieved peak at day 14 after reperfusion. To investigate the possible effects of CD4+ infiltration on the remodelling process and functional recovery, C57BL/6J wild-type (WT) mice and 2D2 mice (transgenic mice carrying a T cell receptor for myelin oligodendrocyte glycoprotein) were subjected to MCAo. CD4+ T cells were depleted by injecting 200ug rat anti-CD4 antibody at day 3, 5, 7, 9 after MCAo. Placebo group was injected with the same dose of isotype matched antibody as control. In contrast to WT mice, CD4 depletion reduced the deposition of collagen I in 2D2 mice. In addition, CD4 depletion diminished the vascular density in the ischemic striatum. In the gait analysis, mice with CD4 depletion had a significantly reduced normalized swing speed of their hind paws on the affected side ($p<0.001$). Our results suggest that CD4 depletion can detrimentally influence both the vascular remodelling and the functional recovery in 60min MCAo mouse model. Nevertheless, more experiments are needed to elucidate the possible cell types or soluble factors modulated by CD4+ T cells in ischemic brain.

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)
Prof. Dr. Wolfgang Brück (Göttingen)

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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
Prof. Dr. med. Dietmar Schmitz

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Graduate Training Program
learning & memory

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
Prof. Dr. Ulrich Dirnagl

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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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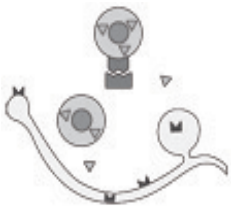

Interdisciplinary Wolfgang Köhler Research Center

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.
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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.

Spokesperson: Prof. Dr. Helmut Kettenmann

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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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