Program Abstracts

BNF2014

Berlin Neuroscience Forum 2014

Congress Hotel Liebenwalde

June 12 - 13, 2014

http://www.bnf-info.de

The Berlin Neuroscience Forum 2012 is a joint activity of

Berlin Neuroimaging Center

Berlin School of Mind and Brain

Bernstein Center for Computational Neuroscience

BMBF Network „ImmunoPain“

BMBF Network „Medical Systems Biology - Nociceptor Inhibition“

Deutsches Zentrum für Neurodegenerative Erkrankungen - Cluster Berlin

DFG-Forschergruppe „Konflikte als Signale“

Exzellenzcluster NeuroCure

Exzellenzcluster Language of Emotion

GRK „Neuropsychiatrie und Psychologie des Alters“

GRK „Zelluläre Mechanismen von Lernen und Gedächtniskonsolidierung hippocampaler Funktion“

Helmholtz International Research School ‚Molecular Neurobiology‘ at the MDC

Helmholtz Virtual Institute „Multifunctional Biomaterials for Medicine“

Leibniz-Institut für Molekulare Pharmakologie

Promotionskolleg „Computational Neuroscience“

SFB „Theoretische Biologie“

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

SFB „Entwicklungsstörungen im Nervensystem“

SFB Transregio „Gehirn als Ziel von entzündlichen Prozessen“

Studiengang „Medizinische Neurowissenschaften“

Zentrum für Schlaganfallforschung (CSB)

Program Committee

Ingolf Blasig
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Poster Jury

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Organization

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Max-Delbrück-Centrum für Molekulare Medizin (MDC) Berlin-Buch
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General Information

Registration and Office Hours	Thursday, June 12, 2014 Friday, June 13, 2014	**11.00 - 20.00** **8.00 - 16:00**
Office Phone	0151 172 197 92	
Poster Boards	Height : 120 cm Width: 100 cm	
Poster Sessions	**Poster Sessions I** Thursday, June 12, 2014	**14:50 - 16:45**
	Poster Session II Friday, June 13, 2014	**13:30 - 15:00**
	Posters can hang during the entire meeting. Please remove all posters before the end of the meeting.	
Duration of Oral Presentations	**Invited Speakers**	30 min (talk) 15 min (disc.)
	Welcome to Berlin Sessions	20 min (talk) 10 min (disc.)
	Young Investigator Presentations	10 min (talk) 5 min (disc.)

Scientific Program

Thursday, June 12, 2014

11.00 – 13.00 **Arrival and Registration**

12.00 – 13.00 **Lunch**

13.00 – 13.05 **Welcome: Helmut Kettenmann**

13.05 – 13.50 **Lecture I**
Chair: Frank Heppner

Tony Wyss-Coray
Stanford, USA
MODULATION OF BRAIN AGING AND PLASTICITY THROUGH SYSTEMIC FACTORS

13.50 – 14.50 **Young Investigator Presentations I**
Chair: Helmut Kettenmann

Angeli Möller
Max-Delbrück-Centrum für Molekulare Medizin (MDC), Neuroproteomics, Berlin
PHOSPHORYLATION-DEPENDENT INTERACTIONS OF MUNC18

Anne Järve
Max-Delbrück-Centrum für Molekulare Medizin (MDC), Molecular Biology of Peptide Hormones, Berlin
EFFECT OF CXCL12 AXIS MODULATION ON IMMUNE CELL RECRUITMENT IN SPINAL CORD, BONE MARROW AND BLOOD FOLLOWING SPINAL CORD INJURY

Anna Carbone
Molecular Neuroscience and Biophysics, Neurocure
SUPERACTIVATION OF AMPA RECEPTORS BY AUXILIARY PROTEINS

Thursday, June 12, 2014

Tatiana Korotkova
Leibniz-Institut für Molekulare Pharmakologie (FMP)
AG Behavioural Neurodynamics Berlin
GAMMA-RHYTHMIC SIGNALING BETWEEN MEDIAL PREFRONTAL CORTEX AND LATERAL SEPTUM

14.50 - 16.45 **Poster Session I and Coffee Break**

16.45 - 17.30 **Lecture II**
Chair: Volker Haucke

Peter Scheiffele
Basel, Switzerland
DECONVOLING MOLECULAR DIVERSITY AND LOGIC OF POLYMORPHIC SYNAPTIC ADHESION MOLECULES

17.30 - 18.30 **Welcome to Berlin Session I**
Chair: Ingolf Blasig

Janine Kirstein-Miles
Leibniz Institute for Molecular Pharmacology (FMP) & NeuroCure Excellence Cluster, Berlin
PROTEOSTASIS IN AGING AND NEURODEGENERATIVE DISEASES

Ursula Koch
Freie Universität Berlin, Institut für Biologie,
AG Neurophysiologie; Berlin
TEMPORAL SOUND PROCESSING IN HEALTH AND DISEASE - FROM SYNAPSES TO CIRCUITS

18.30 - 19.00 **Dinner Talk**
Chair: Benedikt Salmen

Walther Ch. Zimmerli
Humboldt Graduate School Berlin, Berlin
'PURE' BASIC RESEARCH AND 'DIRTY' TECHNOLOGY: MISSUNDERSTANDING SCIENCE

Thursday, June 12, 2014

19.00 - 20.00 **Dinner**

20.00 – 20.45 **Lecture III**
Chair: Hans-Joachim Pflüger

Martin Göpfert
Göttingen, Germany
DROSOPHILA HEARING: MECHANISMS AND GENES

ca. 21.00 **Public Viewing**
2014 FIFA World Cup opening match: Brasil / Croatia

22.00 **Disco Night**

Friday, June 13, 2014

08.00 - 09.00 **Breakfast**

09.00 - 09.45 **Lecture IV**
Chair: Gabriel Curio

Peter König
Osnabrück, Germany
OVERT ATTENTION AS A DECISION PROCESS

09.45 - 11.15 **Welcome to Berlin Session II**
Chair: Helmut Kettenmann

Martin Rolfs
Bernstein Center for Computational Neuroscience Berlin/ Department of Psychology, Humboldt Universität, Berlin
ATTENTIVE PROCESSES IN ACTIVE VISION AND COGNITION

Christian Otte
Charité Universitätsmedizin Berlin, Klinik für Psychiatrie und Psychotherapie, Berlin
NEUROBIOLOGICAL STRESS-SYSTEMS IN DEPRESSION AND ANXIETY

Stefan M. Gold
Center for Molecular Neurobiology, Institute for Neuroimmunology and Multiple Sclerosis, Hamburg
ENDOCRINE-IMMUNE NETWORKS AND NEUROPSYCHIATRIC SYMPTOMSIN CNS AUTOIMMUNITY

11.15 - 11.30 **Coffee Break**

11.30 – 12:30 **Young Investigator Presentations II**
Chair: Malek Bajbouj

Yan Fan
Cluster Languages of Emotion, Freie Universität Berlin
EMOTIONAL ABUSE AND OXYTOCIN MODULATE AMYGDALA-HIPPOCAMPAL CONNECTIVITY CHANGES DURING ACUTE PSYCHOSOCIAL STRESS

Friday, June 13, 2014

Simon Jacob
Department of Psychiatry and Psychotherapy, Charité)
SINGLE NEURON CORRELATES OF EXECUTIVE CONTROL IN THE PRIMATE CORTEX: PHYSIOLOGY AND PHARMACOLOGY

Sandra Wohlgemuth
Department of Psychiatry and Psychotherapy, Charité, Berlin
EFFECT OF FOXP2 ON SYNAPTIC TRANSMISSION AND PLASTICITY IN ZEBRA FINCHES

Lars Winkler
Leibniz-Institut für Molekulare Pharmakologie (FMP), Berlin
THE IMPACT OF CLAUDIN-3 DEFICIENCY ON THE INTEGRITY OF THE BLOOD BRAIN BARRIER

12.30 - 13.30 **Lunch**

13.30 – 15.00 **Poster Session II and Coffee Break**

15.00 – 15.45 **Lecture V**
Chair: Ulrich Dirnagl

Costantino Iadecola
New York, USA
NEUROVASCULAR PATHWAYS TO COGNITIVE DYSFUNCTION: MECHANISMS AND THERAPEUTIC IMPLICATIONS

16.00 **Departure**

List of Poster Presentations

Thursday, June 12, 2014: 14:50 - 16:45

Friday, June 13, 2014: 13:30 - 15:00

1. THE REELIN RECEPTOR VLDLR IS A DIRECT TARGET OF FOXP2 AND REGULATED DEVELOPMENTALLY AND BY SINGING
Adam, I.; Mendoza, E.; Kobalz, U.; Wohlgemuth, S.; Scharff, C.
Animal Behavior, Freie Universität Berlin

2. SPONTANEOUS FIELD POTENTIAL TRANSIENTS IN THE RAT DENTATE GYRUS
Anderson, M.L.; Heinemann U.
Neurophysiology, Charité – Universitätsmedizin

3. NONCANONICAL DOPAMINE-DEPENDENT SYNAPTIC PLASTICITY IN A RODENT MODEL OF ACUTE PSYCHOSIS
Bartsch, J.C.; Fidzinski, P.; Huck, J.H.J.; Hörtnagl, H.; Kovacs, R.; Priller, J.; Wozny, C.; Behr, J.
Psychiatry and Psychotherapy, Charité - Universitätsmedizin Berlin

4. OPTOGENETIC CONTROL OF THETA OSCILLATIONS IN BEHAVING MICE
Bender, F.; Gorbati, M.; Korotkova, T.; Ponomarenko, A.
Behavioural Neurodynamics, FMP

5. IMPLICATIONS OF ENZYME DEFICIENCIES ON MITOCHONDRIAL ENERGY METABOLISM AND REACTIVE OXYGEN SPECIES FORMATION.
Berndt, N.; Bulik, S.; Holzhütter, H.-G.
Institute of Biochemistry, Charité - Universitätsmedizin Berlin

6. CLAUDIN EXPRESSION IN TIGHT JUNCTIONS OF THE BLOOD-BRAIN BARRIER
Berndt, P.; Winkler, L.; Blasig, I. E.
Leibniz-Institut für Molekulare Pharmakologie

7. WHAT CAN WE LEARN FROM THE EXCITATION-INDUCED NAD(P)H RESPONSE OF NEURONAL TISSUES: A MODEL-BASED ANALYSIS.
Berndt, N.; Kann, O.; Holzhütter, H.-G.
Institute of Biochemistry, Charité - Universitätsmedizin Berlin

8. DIFFERENT POPULATIONS OF NEURONS WITH DISTINCT MEMBRANE AND SYNAPTIC PROPERTIES IN THE DORSAL AND VENTRAL PART OF THE VNLL
Caspari, F.; Baumann, V.J.; Garcia-Pino, E.; Koch, U.
Institut für Biologie, Freie Universität Berlin

9. COORDINATION OF INNATE BEHAVIOURS BY GABAERGIC CELLS IN LATERAL HYPOTHALAMUS
Carus-Cadavieco, M.; Gorbati, M.; Ponomarenko, A.; Korotkova, T.
Behavioural Neurodynamics, FMP

10. VALIDATION OF PEPTIDOMIMETICS FOR ENHANCED DRUG DELIVERY THROUGH THE BLOOD-BRAIN BARRIER
Dithmer, S.; Staat, C., Winkler, L., Blasig, I.E.
Leibniz-Institut für Molekulare Pharmakologie

11. MODELING HIPPOCAMPAL RIPPLES IN-VITRO: INTRA-RIPPLE FREQUENCY DYNAMICS AND RESPONSE TO PHARMACOLOGY
Donoso, J.R.; Kempter, R.
Bernstein Center for Computational Neuroscience Berlin

12. TRANSCRIPTIONAL AND EPIGENETIC DYNAMICS DURING ES CELL DIFFERENTIATION IN TO DOPAMINERGIC NEURONS
Ferrai,C.
Epigenetic Regulation and Chromatin Architecture, BIMSB

13. THE D2 RECEPTOR PARTIAL AGONIST 2-BROMOTERGURIDE DOES NOT AFFECT BODY WEIGHT AND BODY FAT COMPOSITION OF RATS
Franke, R.T.; Pertz, H.H.; Fink, H.; Brosda, J.
Veterinary medicine, Institute for Pharmacology and Toxicology

14. CHARACTERIZATION OF CELL-DEATH MECHANISMS WITHIN THE CENTRAL AUDITORY PATHWAY UPON REPEATED NOISE EXPOSURE
Fröhlich, F.; Gröschel, M.; Ernst, A.; Basta, D.
Department of Otolaryngology, Unfallkrankenhaus Berlin, University of Berlin, Charité Medical School, Germany

15. EMOTIONAL STATES AND MEMORY-RELATED EEG OSCILLATIONS
Gärtner, M.; Grimm, S.; Bajbouj, M.
Psychology, FU Berlin

16. JOINT REGULATION OF DEFENSIVE BEHAVIOR AND CIRCULATORY RESPONSES BY HYPOTHALAMIC CIRCUITS
Gao, X; Korotkova,T; Ponomarenko, A.
AG Behavioural Neurodynamics, Leibniz-Institut für Molekulare Pharmakologie (FMP)

17. THE NAKED MOLE RAT AUDITORY BRAINSTEM: AN ANATOMICAL AND NEUROCHEMICAL DESCRIPTION
Garcia-Pino E.; Gessele N.; Thomas Park; Koch U.
Biology, Chemistry, Pharmacy, FU Berlin

18. PANEL REGRESSION MODELING OF OPTOGENETIC INTERROGATION OF NETWORK OSCILLATIONS
Gorbati, M.; Bender, F.; Korotkova, T.; Ponomarenko, A.
Behavioural Neurodynamics, Leibniz-Institut für Molekulare Pharmakologie (FMP)

19. THE TPH2-KNOCKOUT RAT - PHYSIOLOGICAL AND BEHAVIORAL ANALYSIS OF A SEROTONIN DEFICIENT RAT MODEL
Graf, Y.; Beis, D.; Hainer, C.; Holzwarth, K.; Flinders, M.; Swann, V.; Geurts, A.; Hodges, M.; Bader, M.; Wöhr, M.; Alenina, N.
AG Bader - Molecular Biology of Peptide Hormones, Max-Delbrück-Center for Molecular Medicine

20. CALCIUM-RELATED ACTIVITY IN THE CENTRAL AUDITORY SYSTEM AFTER AGE-RELATED OR NOISE-INDUCED HEARING LOSS
Gröschel, M.; Hubert, N.; Müller, S.; Ernst, A.; Basta, D.
Klinik für Hals-, Nasen- und Ohrenheilkunde, Unfallkrankenhaus Berlin

21. THE ROLE OF SEROTONIN IN RUNNING-INDUCED NEURONAL ACTIVITY
Hainer, C.; Klempin, F.; MacMahon, A.; Alenina, N.; Bader, M.
Neurobiology, MDC Berlin

22. FREE RADICAL DEPENDENT NEUROVASCULAR DE-COUPLING IN AN IN VITRO MODEL OF STATUS EPILEPTICUS
Hasam,L.A.; Papageorgiou, I.; Swolinsky, J.; Friedman, A.; Kovács, R.
Institut für Neurolophysiologie, Charité

23. EFFECTS OF BLOOD BRAIN BARRIER DYSFUNCTION ON RESPONSES TO ANTIEPILEPTIC DRUGS
Heinemann, U.; Salar, S.; Maslarova, A.; Kunz, W., Friedman. A.
Institut für Neurophysiologie, Charité Universitätsmedizin Berlin

24. ABNORMAL CENTROSOME AND SPINDLE MORPHOLOGY IN HUMAN CELLS FROM PATIENTS WITH AUTOSOMAL RECESSIVE PRIMARY MICROCEPHALY SUBTYPES
Issa-Jahns, L. ; Gamal Faraq, H. ; Kraemer, N. ; Ravindran, E. ; Stoltenburg-Didinger, G. ; Morris-Rosendahl, D.J. ; Kaindl, A.M.
Charité University Medicine Berlin, Institute of Neuroanatomy and Cell Biology

25. NEURON-ASTROCYTE INTERACTIONS CONTRIBUTE TO CHANGES IN PLASTICITY IN THE HIPPOCAMPUS IN AN ANIMAL MODEL OF POSTTRAUMATIC STRESS
Ivens, S.; Albrecht, A.; Richter-Levin, G., Stork, O., Heinemann, U.
Klinik für Psychiatrie und Psychotherapie, Charité – Universitätsmedizin

26. DEFICIENCIES IN FOLIC ACID AND UNG RESULT IN LEARNING DEFICITS, AND DECREASED MMP-9 LEVELS IN A MOUSE MODEL OF VASCULAR DEMENTIA
Jadavji, NM; Farr, TD, Lips, J; Khalil, A; Boehm-Sturm, P; Harms, C; Foddis, M; Füchtemeier, M; Dirnagl U
Experimental Neurology, Charite University Medicine

27. NOVEL COMPOUNDS TARGETING MICROGLIAL ACTIVATION
Jordan, P; Kleisse, S.; Wolf, S.; Kettenmann, H.
Cellular Neurosciences, Max-Delbrück-Centrum Berlin

28. MINERALOCORTICOID RECEPTOR STIMULATION IMPROVES COGNITIVE FUNCTION AND DECREASES CORTISOL SECRETION IN DEPRESSION AND HEALTH
Kaczmarczyk, M.; Otte, C.; Wingenfeld, K.; Kuehl, L. K.; Hinkelmann, K.
Department of Psychiatry and Psychotherapy, Charité University Medical Center, Campus Benjamin Franklin

29. CDK5RAP2 KNOCKDOWN IN MURINE EMBRYONIC STEM CELLS AFFECTS PROLIFERATION AND NEURAL DIFFERENTIATION, BUT NOT NON-NEURAL DIFFERENT
Krämer, N.; Issa-Jahns, L.; Neubert, G.; Seiler, A.; Ravindran, E.; Ninnemann, O.; Kaindl, A.M.
Institute of Cell Biology and Neurobiology and Department of Pediatric Neurology, Charité - Universitätsmedizin Berlin

30. ENHANCED EMOTIONAL EMPATHY AFTER MINERALOCORTICOID RECEPTOR STIMULATION IN WOMEN WITH BORDERLINE PERSONALITY DISORDER + CONTROLS
Kuehl, L.; Roepke, S.; Janke, K.; Hinkelmann, K.; Otte, C.; Wingenfeld, K.
Department of Psychiatry and Psychotherapy, Charité University Medicine

31. NOVEL FUNCTIONS OF C-JUN N-TERMINAL KINASES IN NEURONS
Kunde, S.A.; Rademacher, N; and Shoichet, S.A.
Neuroscience Research Center, Charité - Universitätsmedizin Berlin

32. MITOCHONDRIAL AND BIOENERGETIC REMODELING WITHIN HUMAN PSC-DERIVED NEURAL PROGENITORS
Lorenz, C.; Pfiffer, V.; Bukowiecki, R.; Wanker, E. E.; Prigione, A.
Neuroproteomics, Max Delbrueck Center for Molecular Medicine (MDC)

33. MINOCYCLINE RESCUES DECREASE IN NEUROGENESIS AND DEFICITS IN SENSORIMOTOR GATING IN AN ANIMAL MODEL OF SCHIZOPHRENIA
Mattei, D.; Djodari-Irani, A.; Hadar, R.; Pelz, A.; de Cossío, LF.; Goetz, T.; Matyash, M.; Kettenmann, H.; Winter, C.; Wolf, SA.
Cellular Neuroscience, MDC

34. THYROID HORMONES INFLUENCE NEURONAL ENERGY METABOLISM VIA THYROID HORMONE TRANSPORTERS
Meyer, F.; Schweizer, U., Wirth, EK
Institut für Experimentelle Endokrinologie, Charité - Universitätsmedizin Berlin

35. AMBIENT GLUTAMATE A TOOL TO DISSECT SYNAPTIC AND EXTRASYNAPTIC NMDA RECEPTOR POPULATIONS IN ACUTE HIPPOCAMPAL SLICES
Moldavski,A.; Bading, H.; Bengtson, C.P.
Charité – Universitätsmedizin Berlin, Department of Neurophysiology, Berlin

36. COMPARISON OF TWO METHODS TO DETERMINE RELATIVE FLAIR SIGNAL INTENSITIES OVER TIME IN ACUTE ISCHEMIC STROKE
Ostwaldt, A.; Galinovic, I.; Hotter, B.; Nolte, C.H.; Audebert, H.; Villringer, K.; Fiebach, J.B.
Center for Stroke Research Berlin, Charité Universitätsmedizin Berlin

37. STUDYING REGENERATION OF THE CORTICOSPINAL TRACT IN ORGANOTYPIC SLICE CULTURES
Pohland, M. ; Glumm, R. , Strauß, U. ; Kiwitt, J. ; Bräuer, A. ; Glumm, J.
Charité - Universitätsmedizin Berlin, Institut für Zell- und Neurobiologie, AG Glumm

38. REGULATION OF PSD-95 COMPLEX ASSEMBLY
Rademacher, N.; Kunde, S.A.; and Shoichet, S.A.
Neuroscience Research Center, Charité - Universitätsmedizin Berlin

39. PREDICTIVE CODING FAILURE EXPLAINS AUDITORY GATING AND MISMATCH NEGATIVITY DEFICITS IN SCHIZOPHRENIA
Rentzsch, J.; Jockers-Scherübl,M.; Gallinat, J.; Christina Shen, H. Neuhaus, A.
Klinik für Psychiatrie und Psychotherapie, Charité - Universitätsmedizin CBF

40. THE EFFECTS OF COMPROMISED BLOOD-BRAIN BARRIER ON PLASTICITY CHANGES AND RESPONSE TO ANTIEPILEPTIC DRUGS IN THE HIPPOCAMPUS
Salar, S.; Lapilover, E.; Maslarova, A.; Lippmann, K.; Friedman, A.; Heinemann, H.
Charité - Universitätsmedizin Berlin, Institute for Neurophysiology

41. HYPEROXIA IMPAIRS POSTNATAL GRANULE CELL DEVELOPMENT IN THE CEREBELLUM
Scheuer, T.; Marggraf, K.; Bührer, C.; Endesfelder, S.; Schmitz, T.
Charité - Universitätsmedizin Berlin, Klinik für Neonatologie

42. CORRELATION OF FLORBETABEN AMYLOID PET IMAGING AND THE AMYLOID PEPTIDE AÁ42 IN THE CEREBROSPINAL FLUID
Schipke, C. G.; Koglin, N.; Stephens, A.; Joachim, L.; Haas, B.; Peters, O.
Neuropathology, Charité - Universitätsmedizin Berlin

43. PROTECTIVE EFFECTS OF MINOCYCLINE ON WHITE MATTER DEVELOPMENT AFTER NEONATAL HYPEROXIA
Schmitz, T.; Krabbe, G.; Matyash, V.; Scheuer, T.; Endesfelder, S.; Christoph Bührer, C.; Kettenmann, H.
Neonatology, Charité University Medicine Berlin

44. QUANTITATIVE ASSESSMENT OF BLOOD-BRAIN BARRIER PERMEABILITY AND CELL DAMAGE AFTER CORTICAL ISCHEMIA - ROLE OF FREE RADICALS
Schoknecht, K.;Prager, O.; Vazana, U.;Friedman, A.;Heinemann, U.
Charité - Universitätsmedizin Berlin, Institute for Neurophysiology

45. DETECTION OF DISTINCT HUMAN HUNTINGTIN PROTEIN SPECIES USING ANTIBODY-BASED ASSAYS
Schormann,E. ; Bukowiecki,R. ; Prigione, A. ; Wanker, E.
Neuroproteomics, Max Delbrueck Center for Molecular Medicine

46. COGNITIVE FUNCTION IN PATIENTS WITH ADDISON'S DISEASE
Schultebraucks, K.; Wingenfeld, K.; Otte, C.; Quinkler, M.
Charité - Universitätsmedizin Berlin, Department of Psychiatry

47. INTERACTION OF THE COHEN SYNDROME-ASSOCIATED PROTEIN COH1 WITH RAB6 EMPHASIZES ITS ROLE FOR GOLGI FUNCTION AND NEURITOGENESIS
Seifert, W.; Kühnisch, J.; Maritzen, T.; Lommatzsch, S.; Zorn, M., Hofmeyer, M.; Hennies, H.; Bachmann, S.; Horn, D.; Haucke, V.
Institut für Vegetative Anatomie, Charité - Universitätsmedizin Berlin – CCM

48. INTERPLAY OF AUTOPHAGY AND HEXOKINASE II AND THEIR ROLE IN NEURONAL CELL PROTECTION
Sünwoldt, J.; Meisel, A.; Mergenthaler, P.
Experimental Neurology, Charité

49. HYPOTHALAMIC THYROID HORMONE SENSING REGULATES TORPOR INDUCTION
Wirth, E.K.; Willershäuser, M.; Meyer, F.; Rijntjes, E.; Hrabe de Angelis, M.; Köhrle, J.; Klingenspor, M.; et al.
Institut für Experimentelle Endokrinologie, Charité - Universitätsmedizin Berlin

50. AUTOSOMAL RECESSIVE PRIMARY MICROCEPHALY, MORE THAN JUST A NEURAL PROGENITOR PROLIFERATION DEFECT?
Zaqout, S.; Krämer, N.; Fassbender, J.; Issa-Jahns, L.; Stoltenburg-Didinger, G.; Kaindl, A.
Anatomy, Cell Biology and Neurobiology

51. SYNAPTIC PLASTICITY INDUCED BY GAMMA FREQUENCY OSCILLATIONS
Zarnadze, S.; Dugladze, T.; Bäuerle, P.; Schmitz, D.; Gloveli, T.
Institute of neurophysiology, Charité Universitätsmedizin Berlin

Abstracts of Plenary Lectures

HEARING IN DROSOPHILA: MECHANISMS AND GENES

Martin Göpfert

Schwann-Schleiden-Center for Molecular Cell Biology

Hearing in Drosophila relies on Johnston's organ neurons in the fly's antenna. These neurons transduce sound-induced antennal vibrations into electrical signals and, in addition, mechanically amplify the vibrations they transduce. Both this transduction and amplification have been traced down to interactions between molecular motors and force-gated ion channels that are mechanically activated by the pull of gating springs. Information about the molecular identities of these motors, channels, and springs will be presented, and the roles of visual opsins in auditory transduction will be discussed: opsins were recently shown to be required for both auditory transduction and amplification, and new data suggests that opsins already serve light-independent sensory functions in the cellular predecessors of Drosophila photoreceptor cells.

NEUROVASCULAR PATHWAYS TO COGNITIVE DYSFUNCTION: MECHANISMS AND THERAPEUTIC IMPLICATIONS

Costantino Iadecola

Feil Family Brain and Mind Research Institute-Weill Cornell Medical College, New York

The brain is uniquely dependent on a well-regulated delivery of oxygen and glucose through the blood supply. If the delivery of cerebral blood flow is not adequate to match the dynamic energetic requirements imposed by neural activity, brain dysfunction and damage ensues Although the mechanisms of the cognitive dysfunction caused by vascular factors (vascular cognitive impairment and dementia) or neurodegeneration (Alzheimer's disease, AD) have traditionally been considered distinct, there is increasing evidence that alterations in cerebral blood flow play a role not only in vascular causes of cognitive impairment, but also in AD. Vascular risk factors and AD impair the structure and function of cerebral blood vessels and associated cells (neurovascular unit), effects mediated by vascular oxidative stress and inflammation. Injury to the neurovascular unit alters cerebral blood flow regulation, depletes vascular reserves, disrupts the blood-brain barrier and reduces the brain's repair potential, effects that amplify the brain dysfunction and damage exerted by incident ischemia and coexisting neurodegeneration. Clinical-pathological studies support the notion that vascular lesions aggravate the deleterious effects of AD pathology by reducing the threshold for cognitive impairment and accelerating the pace of the dementia. In addition, disturbances of cerebral perfusion and/or energy metabolism have also been observed early in the course of AD or even in non-demented subjects at genetic risk for AD. These observations, collectively, indicate that vascular alterations are important both in vascular and neurodegenerative dementias. In the absence of mechanism-based approaches to counteract dementia, targeting vascular risk factors and improving cerebrovascular function offers the opportunity to mitigate the impact of one of the most disabling human afflictions

OVERT ATTENTION AS A DECISION PROCESS

Peter König

Institute of Cognitive Science, University of Osnabrück, Germany

Humans make billions of eye movements in their lifetime that intimately relate action and perception. Each of these entails a decision of how long to linger at a fixated location and where to look next. .Recent technological and algorithmic advances allow the combination of electrophysiological methods (EEG, MEG, fMRI) with the study of eye movements. This has fuelled a fruitful investigation of computational properties and physiological mechanisms of the control of eye movements. In fact, based on the work of recent years we can predict location as well as duration of fixational eye movements to a substantial degree. Furthermore, we dissect the contribution and dynamic interactions of stimulus dependent properties as captured by the concept of saliency map, geometrical constraints like spatial bias and saccadic momentum and task dependent aspects. Finally, we relate these components to the physiological substrate and discuss their relation to general decision processes.

DECONVOLVING MOLECULAR DIVERSITY AND LOGIC OF POLYMORPHIC SYNAPTIC ADHESION MOLECULES

Peter Scheiffele

Biozentrum of the University of Basel, Switzerland and Functional Genomics Center Zurich, Switzerland

The assembly of functional neuronal circuits during development relies on an intricate interplay of cellular interactions, molecular recognition signals, and neuronal activity-dependent processes. Over the past 20 years, families of neuronal cell surface receptors have been identified that may exhibit remarkable molecular diversity. This diversity has been hypothesized to underlie selective trans-cellular interactions and cell-type specific properties, essentially as a molecular code for aspects of neuronal identity. We will discuss recent studies uncovering the molecular coding power of neurexins, one class of polymorphic synaptic receptors. Molecular diversification through extensive alternative splicing makes these proteins candidate molecules for some aspect of neuronal identity, recognition specificity, and/or selective synaptic properties. Combinatorial use of alternative splice insertions in six primary neurexin transcripts generates potentially thousands of distinct isoforms. However, due to major limitations in existing transcript analysis methods it has been impossible to interrogate combinatorial rules of these splicing events. We applied a third-generation sequencing approach on the PacBio platform for comprehensive analysis of combinatorial splice insertion usage in neurexin mRNAs. We discovered novel alternatively spliced segments in Nrxn1 and 3 and identified RNA-binding proteins that give insight into the cell-type specific rules and logic of neurexin isoforms expression. In combination, our studies demonstrate that molecular mechanisms engrave a biased neurexin repertoire on genetically identified cell populations.

Support: Swiss National Science Foundation, EU FP7 Marie Curie & Innovative Medicines Initiatives'

MODULATION OF BRAIN AGING AND PLASTICITY THROUGH SYSTEMIC FACTORS

Tony Wyss-Coray

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Growing evidence links neurodegeneration with altered immune responses not only in the brain but in the periphery as well. In addition, age is the main risk factor for sporadic forms of neurodegenerative diseases, and aging of peripheral organs may affect brain function. How the systemic environment affects brain health is largely unknown and while some of these interactions may involve cells entering the nervous tissue it is likely that others are mediated by soluble factors. We use a combination of physiological methods to manipulate systemic aging and proteomic methods to try to identify factors that age or potentially rejuvenate the brain. Our findings point to systemic changes in immune responses and cellular signaling factors with aging and may be relevant for our understanding of age-related neurodegeneration.

Abstracts of Welcome to Berlin Presentations

ENDOCRINE-IMMUNE NETWORKS AND NEUROPSYCHIATRIC SYMPTOMS IN CNS AUTOIMMUNITY

Stephan Gold

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Major depressive disorder (MDD) has a point prevalence of 13-30% and a lifetime risk of 25-50% in patients with multiple sclerosis (MS) and has a significant impact on cognitive function, quality of life, work performance, and treatment compliance. Despite its immediate clinical relevance, the underlying causes for the high frequency of neuropsychiatric symptoms in MS are poorly understood. One possibility is that depression may be directly linked to pathogenetic processes of MS itself. To test this hypothesis, we examine neuroendocrine-limbic and inflammatory pathways as a potential link between CNS inflammation and depressive symptoms in clinical studies as well as animal models. Using high-resolution magnetic resonance imaging (MRI), we have found that neuroinflammatory damage to brain structures such as the hippocampus, particularly in the subfields cornu ammonis 2-3 and dentate gyrus, may contribute to the development of depression. Moreover, we have found evidence for elevated stress hormone levels, increased cytokine production, as well as disturbed endocrine regulation of T cell function in depressed MS patients. These findings illustrate how studying brain-immune interactions in this disorder can provide valuable clues into the complex relationship between of neuroinflammation and psychopathology.

PROTEOSTASIS IN AGING AND NEURODEGENERATIVE DISEASES

Janine Kirstein-Miles

Leibniz Institute for Molecular Pharmacology (FMP) + NeuroCure Excellence Cluster

All the information required for the folding of proteins into functional native three-dimensional conformations is encoded in the primary amino acid sequence. However, the folding and stability of the native state can be challenged by the crowded cellular environment as well as by accumulation of random errors during protein biogenesis. This will often lead to the formation of metastable proteins that can readily misfold and aggregate. The tendency of disease-associated aggregation-prone proteins to misfold and aggregate is strongly enhanced during aging. The accumulation of damaged proteins is a well-established marker of aging, and this disruption of proteostasis is further amplified during aging. Moreover, protein aggregates are a hallmark of neurodegenerative diseases such as Alzheimer's, Huntington's and Parkinson's disease. The cellular proteostasis network integrates the protein folding and clearance machineries across multiple subcellular compartments of the eukaryotic cell. The ER, for example, is the site for synthesis and folding of membrane proteins and the secretory pathway. A distinctive feature of the ER is a tightly controlled redox homeostasis for the formation of inter- and intra-molecular disulfide bonds. Employing genetically encoded in vivo sensors reporting on the organelle-specific redox state, we could show that the redox state of the ER is subject to profound changes during the lifetime of an animal. Surprisingly, aging is associated with a shift towards reducing conditions in the ER coinciding with the onset of fecundity. Moreover, we can show that the presence of protein aggregates such as those formed by polyQ, Aβ and artificial β-sheet proteins in the cytosol is associated with a collapse of the redox homeostasis in the ER in the nematode model as well as in mammalian cells. An inhibition of the proteasome further contributes to an accumulation of misfolded and aggregated endogenous proteins and consequently is associated with a shift towards reducing conditions in the ER. Interestingly, the redox state in the cytosol responds to proteotoxic challenges in an opposing manner and becomes more oxidized during aging and upon stress. Our observations indicate that a balanced protein homeostasis is necessary for ER and cytosolic redox homeostasis and that cellular stresses can be transmitted in a cross-compartmental manner. Moreover, the organellar redox homeostasis can also be challenged by trans-tissue imbalances of proteostasis. Proteotoxic perturbations in neuronal cells affect the redox state of a non-stressed distal tissue such as muscle.

TEMPORAL SOUND PROCESSING IN HEALTH AND DISEASE - FROM SYNAPSES TO CIRCUITS.

Ursula Koch

Freie Universität Berlin, Institut für Biologie, AG Neurophysiologie

Analyzing the temporal structure of sounds is essential for sound recognition including the understanding of speech. I am interested in how neural circuits in the auditory brainstem are set-up to extract the temporal information of sounds and what internal and external factors shape their development. Distinct neural circuits in the auditory brainstem (e.g. the lateral superior olive and the ventral nucleus of the lateral lemniscus) integrate precisely timed excitatory and inhibitory information to extract information about the temporal patterns of sounds. The output response of these neurons either mirrors the temporal sound pattern or, at the next stage, they selectively respond to specific sound patterns. On the cellular level these neurons receive large and precisely timed excitatory and inhibitory inputs. In addition, these neurons possess membrane properties that enable an accurate integration of input patterns including extremely large voltage-gated currents. These specialized synaptic and network properties emerge and refine during the first weeks postnatally and are dependent on proper auditory experience. Apart from sensory experience auditory processing may also be altered by environmental or genetic manipulation. We investigate to what extent synaptic transmission and integration is altered e.g. in autistic mouse model and correlate this to disturbances in auditory processing and perception.

NEUROBIOLOGICAL STRESS-SYSTEMS IN DEPRESSION AND ANXIETY

Christian Otte

Charité Universitätsmedizin Berlin, Klinik für Psychiatrie und Psychotherapie

Alterations of two major neurobiological stress-systems, the autonomous nervous system (ANS) and the endocrine hypothalamus-pituitary-adrenal (HPA) axis play a major role in different aspects of depression and anxiety. This talk will discuss how the ANS and HPA axis

- are involved in the etiology of depression and anxiety
- contribute to an increased risk of cardiovascular disease in patients with depression and anxiety
- are associated with cognitive function
- might be addressed as therapeutic targets in pharmacological and non-pharmacological interventions

ATTENTIVE PROCESSES IN ACTIVE VISION AND COGNITION.

Martin Rolfs

Bernstein Center for Computational Neuroscience Berlin, Department of Psychology, Humboldt Universität zu Berlin

Eye and head movements shape how we perceive the world around us. With no apparent effort, they select relevant data from a rich visual environment.Goal-directed saccadic gaze shifts are swift and efficient, but they also cause challenges for the visual system. Objects that have fixed places in the world rapidly slip across the retina several times per second. In our group, we use a combination of motion-tracking, visual psychophysics, and computational modeling to investigate the role of attention in maintaining the continuity of visual perception and cognition across of eye and head movements. In my presentation, I will first give an overview of the influences of goal-directed movements on visual attention and perception and then focus on an ongoing study investigating the impact of saccades on visual short-term memory (VSTM). VSTM allows us to recall what we have just seen when the sensory input has disappeared from view, and many psychophysical studies have revealed its fragile nature. We show that memory performance is enhanced for test stimuli that had appeared at the target of a saccadic eye movement that was itself planned and executed after the disappearance of the visual stimulus array,. This was true despite the fact that saccades went as often to the test location as to any other location in the array. A simple model of memory performance revealed that items at non-target locations were forgotten more often (reduced quantity), but that successfully remembered items were retained with a similar degree of fidelity irrespective of whether the saccade had targeted its location (comparable quality). This strong impact of saccadic eye movements on VSTM highlights the crucial impact of action on which parts of a scene we remember and which we forget

Abstracts of Oral Presentations

SUPERACTIVATION OF AMPA RECEPTORS BY AUXILIARY PROTEINS

Anna Carbone

NeuroCureCharité-Universitätsmedizin, FMP Berlin, Germany

AMPA receptors (AMPARs) mediate most of the fast excitatory synaptic transmission in the brain. At synapses, AMPARs form macromolecular complexes that include auxiliary subunits, such as Transmembrane AMPA receptor Regulatory Proteins (TARPs).TARPs control the activity of AMPARs during fast synaptic transmission through a seemingly bewildering array of effects. The functional properties of AMPARs expressed at synapses shape synaptic currents and contribute to the short-term plasticity of the synaptic response. Determining the factors that control the gating of AMPARs is therefore crucial to understanding how neurons process information. Several models have been proposed to explain the mechanism of action of TARPs on AMPARs. However, none of these proposed mechanisms was able to fully describe the behaviour of these complexes. In order to better understand how TARPs modulate AMPARs we used GluA2 mutants,which spend very different fractions of time in desensitised state. Kinetic analysis showed that TARPs had a limited effect on mutants with a long-lived desensitised state. In contrast, mutants with unstable desensitised states showed profound modulation by TARPs. These results suggest that TARPs exert their effects principally on the open state of the receptor. We propose a simple model based on the ideathat because TARPs promote channel opening, receptor activation promotes AMPAR-TARP complexes into a superactive state with high open probability. This modelpredicts all known effects of TARPs on AMPA receptor function also unexpected phenomena including massive potentiation in the absence of desensitization and supramaximal recovery that we subsequently detected in electrophysiological recordings. The transient positive feedback mechanism that we demonstrate has implications for information processing in the brain, because it would allow activity-dependent facilitation of excitatory synaptic transmission through a purely postsynaptic mechanism.

EMOTIONAL ABUSE AND OXYTOCIN MODULATE AMYGDALA-HIPPOCAMPAL CONNECTIVITY CHANGES DURING ACUTE PSYCHOSOCIAL STRESS

Yan Fan

Cluster Languages of Emotion, Freie Universität Berlin

Background: Previous evidence shows that acute stress changes both amygdala activity and connectivity with a distributed brain network (1). Early life stress (ELS) is associated with altered stress responsiveness in later life (2). However, it remains unclear whether ELS can modulate stress-induced changes in amygdala connectivity. Our recent findings show that oxytocin (OXT) attenuates stress response in subjects without a history of ELS, but enhances stress response in subjects with a history of ELS (3). Here we investigate the effect of ELS and OXT on transient changes of amygdala connectivity induced by acute psychosocial stress. Methods: Thirty-two healthy young males participated in an fMRI study of psychosocial stress. Each subject was administered oxytocin and placebo in two separate sessions, with sequences counter-balanced across subjects. Results: Psychophysiological interaction (PPI) analysis in the placebo session revealed stress-induced increases in functional connectivity between amygdala and medial prefrontal cortex, posterior cingulate cortex, putamen, caudate and thalamus. Regression analysis showed that emotional abuse (EA) was inversely associated with stress-induced changes in connectivity between right amygdala and right hippocampus. Moreover, hierarchical linear regression showed that OXT attenuated stress-induced positive amygdala-hippocampal connectivity in subjects with high EA scores, as well as negative connectivity in subjects with low EA scores. Amygdala-hippocampal connectivity in the OXT session correlated negatively with cortisol response. Conclusion: These findings indicate that the amygdala-hippocampal circuit plays crucial role in the interplay between stress reactivity, ELS and the effect of OXT.

SINGLE-NEURON CORRELATES OF EXECUTIVE CONTROL IN THE PRIMATE CORTEX: PHYSIOLOGY AND PHARMACOLOGY

Simon Jacob

Department of Psychiatry and Psychotherapy, Charité – Universitätsmedizin Berlin

The primate lateral prefrontal cortex (PFC) and posterior parietal cortex (PPC) are major nodes in a brain network that supports high-level cognitive functions. I will present recent experiments performed in awake behaving rhesus monkeys that address how single neurons in these brain regions give rise to intelligent, goal-directed behavior. In the first part of the talk, I challenge the commonly held view that suppression of distractors by PFC neurons is the main mechanism underlying the neural filtering of task-irrelevant information. The data instead suggest that distractors can be bypassed by storing and retrieving information through fronto-parietal cooperation. In the second part of the talk, I demonstrate that prefrontal processing is strongly modulated by dopamine, a neurotransmitter linked to mental disorders such as schizophrenia. The data show that dopamine controls sensory processing and perceptual decision-making by modulating distinct classes of prefrontal single neurons. In summary, I will argue that the combination of single-unit recordings and neuropharmacological tools in awake trained animals is a promising approach to elucidate the neuronal mechanisms that underlie complex behavior in the healthy and diseased brain.

EFFECT OF CXCL12 AXIS MODULATION ON IMMUNE CELL RECRUITMENT IN SPINAL CORD, BONE MARROW AND BLOOD FOLLOWING SPINAL CORD INJURY IN MOUSE

Anne Järve

Max-Delbrück-Center for Molecular Medicine (MDC), Berlin, Germany

Spinal cord injury (SCI)-associated inflammation is both detrimental by promoting secondary injury, and beneficial by promoting repair depending on subsets and the activation status of the infiltrating cells. Classically activated (M1), pro-inflammatory, macrophages are neurotoxic, whereas alternatively activated (M2) macrophages are growth promoting. Similarly, pro-inflammatory and anti-inflammatory neutrophils were identified in neuronal injury model recently. Because the M2 macrophage response is only transient explaining the limited repair, it is important to determine which signals drive the activation/maintenance as well as migration of M2 type macrophages. The chemokine stromal cell-derived factor 1 (SDF-1/CXCL12) is one of the most potent chemotactic factors, released at the injury site. Here, we investigate the role of CXCL12 and its receptors CXCR4 and CXCR7 in recruitment and activation state of neutrophils, monocytes, macrophages in spinal cord, bone marrow and peripheral blood in mouse dorsal compression SCI model. Animals received 1) injections of CXCR7 inhibitor CCX771; 2) injections of CXCR4 inhibitor AMD3100 or 3) intrathecal infusion of CXCL12 or corresponding vehicles for 7 days, after which FACS analysis was performed. First results of peripheral blood indicate rather similar action of AMD3100 and CCX771 in decreasing the percentage of lymphocytes and elevating the percentage of granulocytes in the blood which is in contrast to the animals which received SDF-1 infusion. Analysis and spinal cord tissue and bone marrow will reveal the entire complexity of the regulation of immune reaction via CXCL12 axis.

GAMMA-RHYTHMIC SIGNALING BETWEEN MEDIAL PREFRONTAL CORTEX AND LATERAL SEPTUM IN BEHAVING MICE

Tatiana Korotkova

Leibniz-Institut für Molekulare Pharmakologie (FMP).AG Behavioural Neurodynamics, Berlin

While animal behavior relies on processing of environmental cues and signals about bodily state, physiology of their coordination and control remains poorly understood. Hippocampal and cortical information is relayed to hypothalamus and midbrain mainly via the lateral septal nucleus (LS). We used high-density recording of neuronal discharge and local field potentials (LFP) and in behaving mice as well as computational network modeling to study network synchronization in LS and its afferent regions. LS displayed intermittent state-dependent LFP oscillation in the 30-90 Hz frequency band. Gamma oscillations in LS were synchronized within the nucleus, entrained local neuronal discharge and were coordinated with gamma-synchronization in the medial prefrontal cortex (mPFC). In contrast, hippocampal and LS LFP were coherent preferentially in the theta (5-10 Hz) band. Computational modeling of LS network revealed that strong inhibitory and weak electrical connectivity between local neurons are crucial for gamma generation. Remarkably, individual LS cells displayed relatively low participation rates in gamma oscillations both in experiments and simulations suggesting a weak ING-like generation mechanism. Simulated LS gamma oscillations were readily entrained by weak gamma oscillating inputs when no concurrent theta rhythmicity was present.

Strong theta rhythmic inputs synchronized simulated LS cells at theta frequency, owing to long lasting adaptation currents, reported earlier in LS cells. Recordings in novel and familiar environments showed experience-dependence of fast network synchrony in LS suggesting that LS gamma oscillations can be instrumental in shaping behavioral responses to novelty processed by the upstream cortical regions.

PHOSPHORYLATION-DEPENDENT INTERACTIONS OF MUNC18

Angeli Möller

Max-Delbrück-Centrum für Molekulare Medizin (MDC), Neuroproteomics

The presynaptic protein Munc-18 was initially characterised as binding to the SNARE protein Syntaxin-1, preventing it from forming the SNARE complex, which enables synaptic vesicle exocytosis. However, Munc18 was also shown to be essential for synaptic activity, as evidenced by the synaptically "silent" Munc18 knockout mouse. More recent studies indicate that Munc18 itself may bind the SNARE complex. Using a split-ubiquitin Yeast-3-hybrid assay we have identified pre-synaptic proteins capable of binding to Munc18 in a phosphorylation dependent manner. These interactions were verified in a FRET-based assay in mammalian cells treated with a PKCα activator (PMA). Our results indicate that phosphorylation of Munc18 plays a role its association with the SNARE complex. This would fit with published data that shows the synapses expressing phospho-dead Munc18 cannot induce exocytosis following stimulation with PMA, unlike synapse expressing wild-type munc18.

THE IMPACT OF CLAUDIN-3 DEFICIENCY ON THE INTEGRITY OF THE BLOOD BRAIN BARRIER

Lars Winkler

Leibniz-Institut für Molekulare Pharmakologie (FMP), Berlin

The blood brain barrier (BBB) is the border control of the brain regulating the entry of substances between the circulating blood and the central nervous tissue. This barrier is formed by endothelial cells lining the inner blood vessel lumen and their tight junctions (TJ) sealing the paracellular cleft between those cells. In the TJs of the BBB the transmembrane proteins claudin (Cld) 3, 5 and 12 form one of the tightest barriers of the body. Besides Cld5, which seals the BBB for small molecules, Cld3 is thought to play a crucial role in regulating the barrier permeability especially under pathological conditions where expression of Cld3 is diminished. Therefore, we expected a life threatening increase of BBB permeability in Cld3 deficient mice. Indeed, we found increased permeability of the BBB for sodium Fluorescein (376 Da) and horse radish peroxidase (44 kDa) without elevated brain water content for the knock-out animals. In line with the permeability, the expression of TJ proteins is changed and the TJ strand network is simplified without breaking down completely. Those observations are similar as for the Cld5 deficient mice investigated by others, but instead dying within 10 h after birth the Cld3 deficient mice showed no phenotype at all until two years of age. Hence, we applied pathological conditions first on isolated capillaries of Cld3 deficient mice. The effect of hypoxia on expression and mislocalization of other TJ proteins was significantly increased for capillaries from Cld3 deficient mice pointing towards higher instability of TJs lacking Cld3. In the moment experiments validating the effect of ischemia (middle cerebral artery occlusion) on the BBB lacking Cld3 are preformed.

EEFFECT OF FOXP2 ON SYNAPTIC TRANSMISSION AND PLASTICITY IN ZEBRA FINCHES

Sandra Wohlgemuth

Institut für Verhaltensbiologie, Freie Universität Berlin

Vocal learning in songbirds depends on a specialized pathway through the basal ganglia, including the striatal song nucleus, Area X. The vast majority of neurons in this nucleus are spiny neurons, which receive pallial and dopaminergic inputs providing a candidate substrate for tuning the motor output to the tutor model during song learning. We examined plasticity at glutamatergic synapses of spiny neurons in a slice preparation of Area X from juvenile male zebra finches during the song learning period. High-frequency stimulation of afferent inputs to spiny neurons paired with postsynaptic depolarization induced depression of glutamatergic synaptic transmission, consistent with limited previous data. Responses recovered to baseline levels within 15 minutes in some neurons but persisted for up to 30 minutes in others. The synaptic depression was associated with an increased paired-pulse ratio, which suggests a presynaptically mediated mechanism. Bird song as well as speech learning require adequate amounts of the transcription factor FoxP2. We have previously shown that deficits in vocal learning occur after experimental reduction of FoxP2 in Area X.

Thus, we are also investigating a possible link between FoxP2 levels and synaptic plasticity at Area X spiny neurons, consistent with findings in mouse models. To elucidate the effects of FoxP2 on synaptic transmission and on synaptic plasticity we are analyzing Area X slice preparations of young zebra finches previously injected in one hemisphere with virus mediating FoxP2 knockdown and control virus in the other hemisphere. The FoxP2 knockdown cells show impaired synaptic plasticity and increased NMDA/AMPA ratios compared to control cells. Our results promise insight into the impact of pathological altered FoxP2 levels on physiological mechanisms underlying vocal learning.

Poster Presentations

Thursday, June 12, 2014: 14:50 - 16:45

Friday, June 13, 2014: 13:30 - 15:00

1 THE REELIN RECEPTOR VLDLR IS A DIRECT TARGET OF FOXP2 AND REGULATED DEVELOPMENTALLY AND BY SINGING

Adam, I.; Mendoza, E.; Kobalz, U.; Wohlgemuth, S.; Scharff, C.
Animal Behavior, Freie Universität Berlin

Mutations of the transcription factor FOXP2 lead to severe speech and language impairments in humans. Structural as well as functional imaging studies indicate that the striatal basal ganglia are especially affected by the mutation. The FOXP2 gene codes for a transcription factor, which is strikingly conserved among vertebrates regarding its sequence as well as its expression pattern. In zebra finches it is expressed in the striatal song nucleus Area X which is necessary for song learning and maintenance. In juvenile males FoxP2 is differentially regulated during song learning and in adults by singing. Down-regulation leads to impaired song learning, affects spine formation and prevents social context induced song plasticity. So far no direct target gene relevant for song learning and song production has been described. Here we show that the Reelin receptor VLDLR is co-regulated with FOXP2 during song learning and following adult song performance. FOXP2 bound to the VLDLR promoter and activated it in vitro. Finally we show that experimental down-regulation of FOXP2 in Area X of juvenile males led to down-regulation of VLDLR, consistent with a potential role in song learning and production.

2 SPONTANEOUS FIELD POTENTIAL TRANSIENTS IN THE RAT DENTATE GYRUS

Anderson, M.L.; Heinemann U.
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The idea that the dentate gyrus (DG) functions as a gate has been around for roughly 50 years, in part suggested by its wall-like position between the entorhinal cortex and the hippocampus (HC) as well as its lamellar organization. In acute ventral rat brain slices, the DG shows a small amplitude spontaneous aphasic rhythm of ~0.7 - 1 Hz (Colgin et al. 2004) termed dentate waves (DWs) whose function and underlying network mechanisms remain mostly unsolved. Using extracellular recording techniques combined with pharmacology and laminar profiles, we show that a DG intrinsic network drives this rhythm that is crucially depending on excitatory synaptic transmission and phasic inhibition. We identified a pacemaking mechanism responsible for its timing that involves HCN channels, T-type Ca2+ channels and the persistent Na current. Synaptic transmission at giant mossy fiber boutons also proves to be crucial to maintain this rhythm. Interestingly, there is a correlation between the appearance of DWs and sharp wave-ripples in area CA3 of the HC, which have been shown to be crucial for memory consolidation.

3 NONCANONICAL DOPAMINE-DEPENDENT SYNAPTIC PLASTICITY IN A RODENT MODEL OF ACUTE PSYCHOSIS

Bartsch, J.C.; Fidzinski, P.; Huck, J.H.J.; Hörtnagl, H.; Kovacs, R.; Priller, J.; Wozny, C.; Behr, J.
Psychiatry and Psychotherapy, Charité - Universitätsmedizin Berlin

Dopaminergic hyperfunction and NMDA receptor hypofunction have both been implicated in psychosis. Dopamine-releasing drugs and NMDA receptor antagonists can replicate symptoms associated with psychosis in healthy humans and exacerbate symptoms in patients with schizophrenia. Though hippocampus-dependent cognitive dysfunction is core to acute psychosis, the impact of NMDA receptor hypofunction on hippocampal plasticity remains poorly understood. In the present study, we used the MK-801 model of psychosis to investigate hippocampal long-term potentiation (LTP) in brain slices of Wistar rats. We unveil a novel region-specific form of hippocampal LTP restricted to subicular burst-spiking pyramidal cells. Using sharp microelectrode recordings, whole-cell patch-clamp recordings and Ca2+ fluorescence imaging, we identify a presynaptic form of NMDA receptor-independent LTP that is induced by activation of D1/D5 dopamine receptors and dependent on L-type voltage-gated Ca2+ channels. This cellular mechanism might represent a biological correlate for hippocampus-dependent cognitive deficits in acute psychosis. Thereby, this noncanonical LTP links glutamatergic and dopaminergic pathophysiological concepts of psychosis at the cellular level and suggest L-type voltage-gated Ca2+ channels as a potential target for treatment of cognitive dysfunction in psychosis.

4 OPTOGENETIC CONTROL OF THETA OSCILLATIONS IN BEHAVING MICE

Bender, F.; Gorbati, M.; Korotkova, T.; Ponomarenko, A.
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The activity of large neuronal populations at various time scales is organized by hippocampal network oscillations which are important for cognitive processes. Hippocampal theta oscillations (5-10 Hz) in rodents occur during exploration and REM sleep, organize neuronal discharge and are implicated in spatial navigation and memory. Yet the role of theta oscillations in shaping spatial behavior remains elusive since until recently theta rhythm could not be manipulated in behaving animals. In this study we combined optogenetic control of theta rhythm generators, medial septum and hippocampus, with electrophysiological monitoring of hippocampal network oscillations and neuronal activity. Excitatory (ChR2, ChETA) or inhibitory (halorhodopsin) opsins were expressed locally in hippocampus or in the medial septum in wild-type and parvalbumin-Cre mice. Hippocampal theta oscillations were controlled by optostimulation of septo-hippocampal projections. Peak of power spectral density of optogenetically paced theta oscillations matched stimulation frequency. This allowed us to interfere with the rhythm generation in vivo while monitoring mouse behavior as well as neuronal network- and single cell activity. We implement this approach to study the role of hippocampal theta oscillations in spatial navigation.

5 IMPLICATIONS OF ENZYME DEFICIENCIES ON MITOCHONDRIAL ENERGY METABOLISM AND REACTIVE OXYGEN SPECIES FORMATION

Berndt, N.; Bulik, S.; Holzhütter, H.-G.
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Mitochondrial dysfunction plays a key role in ageing and the dependent development of neurodegenerative diseases and radical oxygen species (ROS) are believed to play key roles in its genesis. In Parkinsons disease activity of the α-ketoglutarate dehydrogenase complex (KGDHC) and complex I of the respiratory chain (RC) are especially affected. We developed a detailed kinetic model of the neuronal mitochondrial energy metabolism to elucidate the interplay between diminished KGDHC activity, mitochondrial ATP generation, redox state, mitochondrial transmembrane potential, and generation of reactive oxygen species (ROS) by the respiratory chain (RC). We investigated the reduction state of those sites of the RC proposed to be involved in ROS production and identified the probable ROS producers for the different RC complexes. Furthermore we investigated the separate effect of complex I or KGDHC inhibition on energy production and the formation of reactive oxygen species (ROS). We than applied the model to a situation where both KGDHC and complex I exhibit reduced activities as in Parkinsons disease. These calculations reveal synergistic effects with respect to the energy metabolism but antagonistic effects with respect to ROS formation:

the drop in the ATP production capacity is more pronounced at a combined inhibition, while the reduction state of the ROS-generating sites of the impaired complex I becomes significantly lowered if additionally the activity of the KGDHC is reduced.

6 CLAUDIN EXPRESSION IN TIGHT JUNCTIONS OF THE BLOOD-BRAIN BARRIER

Berndt, P.; Winkler, L.; Blasig, I. E.
Leibniz-Institut für Molekulare Pharmakologie

The blood-brain barrier protects the brain from harmful components in the circulating blood. This barrier is mainly formed by tight junctions between neighboring endothelial cells that line cerebral microvessels. Consisting of integral membrane proteins including claudins, occludin, tricellulin and junctional adhesion molecules tight junctions regulate the paracellular transport of most molecules. Considering the different barrier characteristics of endothelia and epithelia in various tissues and pathologies we are aiming to clarify the contribution of functionally different claudins to brain endothelial tight junctions. These tight junction proteins exhibit either paracellular tightening or pore-forming potential. We characterized the gene expression level of all claudins in mouse brain capillaries. Among claudin-1, -3, -5 and -12 known to be present in the blood-brain barrier the highest mRNA content was detected for claudin-5. Claudin-3 was found to be expressed 300-fold less than claudin-5 at the lowest level. Additionally we identified six new members of this family to be expressed at a level above that of claudin-3. Among these proteins mostly described to tighten the paracellular cleft we found the newly identified claudin-25 to be highly expressed. Selected claudins were analyzed in their protein expression via western blot using a recombinant expressed standard with equal antibody affinity. This technique was developed to quantify proteins even in the low-femtogram-level. The concentration of claudin-5 with around 800 fmol/µg is 40-fold higher than that of claudin-1 and -12. Relative protein and mRNA expression were found to be not significantly different within the claudin family. The characterization of the tight junction complex which will include further analyses via superresolution microscopy as well as binding studies of identified claudins with other tight junction proteins is especially important to understand the molecular changes underlying pathologies known to compromise the integrity of the blood-brain barrier.

7 WHAT CAN WE LEARN FROM THE EXCITATION-INDUCED NAD(P)H RESPONSE OF NEURONAL TISSUES: A MODEL-BASED ANALYSIS

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NAD(P)H fluorescence is one of the few metabolic signals that enables a local, non-invasive and time-resolved monitoring of the energetic status of mitochondria. In excitable tissues (muscle & nervous system) the NAD(P)H response elicited by an excitatory stimulus frequently displays a bi-phasic characteristics consisting of an initial dip and a subsequent overshoot. Various biochemical and biophysical processes may contribute to this characteristics: Depolarization of the inner mitochondrial membrane owing to an increased calcium uptake, activation of NAD(P)H producing enzymatic reactions in the TCA cycle, oxygen depletion (hypoxia) or increased oxidative phosphorylation. In order to evaluate the relative impact of different biochemical/biophysical processes on the observed NAD(P)H response we have performed computer simulations based on a detailed mathematical model of the energy metabolism of a representative neuronal cell. These simulations permitted to unravel the chain of molecular events underlying a specific observed patterns of the NAD(P)H response. All experimentally determined NAD(P)H profiles could be reproduced by the model indicating that they may arise from one and the same neuronal cell type. Our computations revealed that cells with quite different metabolic status may generate almost identical NAD(P)H signals. Thus an unequivocal physiological interpretation of cumulative NAD(P)H profiles monitored in brain regions encompassing hundreds or thousands of individual cells appears to be problematic. Nevertheless, presence of hypoxic tissue regions comprising cells with strongly restricted oxidative phosphorylation capacity but a Ca2+-activated TCA cycle should be visible from the early onset of the overshoot phase during excitation. Taken together, our computational study allows to a better mechanistic understanding of the metabolic changes underlying NAD(P)H fluorescence profiles.

8 DIFFERENT POPULATIONS OF NEURONS WITH DISTINCT MEMBRANE AND SYNAPTIC PROPERTIES IN THE DORSAL AND VENTRAL PART OF THE VNLL OF MICE

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Neurons in the ventral nucleus of the lateral lemniscus (VNLL) show mixed responses to sounds in terms of temporal response pattern and binaurality. Anatomical studies suggest that at least a subset of ventrally located VNLL neurons receives a major excitatory input that arises from the contralateral ventral cochlear nucleus and inhibitory inputs coming from the ipsilateral trapezoid body. To identify whether different neuron types and inputs are systematically distributed within the VNLL, we characterized the membrane and synaptic properties of VNLL neurons relative to their location within the VNLL. Membrane and synaptic properties of VNLL neurons were characterized by patch-clamp recordings in acute brain slices from P22/23 C57Bl6J mice. Standard immunohistochemistry of perfusion fixed brain sections was performed using antibodies against HCN1, VGluT1 and Calretinin. Based on the immunolabelling pattern against HCN1 and VGluT1, the VNLL could be divided into a ventral (vVNLL) and dorsal part (dVNLL). Neurons in the vVNLL displayed an onset-type firing pattern. These neurons had small Ih amplitudes and a weak HCN1 immunostaining. Fiber stimulation evoked extremely large excitatory synaptic currents that were all-or-none. In contrast, neurons in the dVNLL exhibited two types of firing patterns: onset-type and sustained firing pattern. Both neuron types had a significantly larger isolated Ih. Moreover, dVNLL neurons received 2-7 excitatory inputs. Inhibitory and excitatory inputs to vVNLL neurons had faster rise and decay times. Our results show two distinct areas in the VNLL based on membrane and synaptic properties. This suggests that the vVNLL and dVNLL might play different roles in respect to auditory information processing.

9 COORDINATION OF INNATE BEHAVIOURS BY GABAERGIC CELLS IN LATERAL HYPOTHALAMUS

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Lateral hypothalamus (LH) is crucial for the regulation of innate behaviors, including Food intake and sleep-wake cycle yet temporal coordination of hypothalamic neuronal populations remains elusive. Here we used combination of high-density electrophysiological recordings and optogenetics in behaving mice to study function of GABAergic cells in LH. Excitatory (ChETA) or inhibitory (halorhodopsin) opsins were expressed in LH of VGAT-Cre mice to ensure selective targeting of GABAergic cells. Recordings of neuronal activity and optostimulation were performed in various behavioral paradigms assessing innate behaviours, including a „free-will“ environment where an animal could choose between compartments with food, water, enriched environment and home-cage like enclosure. We found that neuronal activity of GABAergic cells in LH is state-dependent. Optostimulation of GABAergic LH cells at various frequencies as well as stimulation of projections of these neurons changed transitions between innate behaviors.

10 VALIDATION OF PEPTIDOMIMETICS FOR ENHANCED DRUG DELIVERY THROUGH THE BLOOD-BRAIN BAR-

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The blood-brain barrier (BBB) is a diffusion barrier being crucial in controlling the exchange of substances of the circulating bloodstream and the central nervous system (CNS). The BBB is formed by brain endothelial cells, astrocytes, and pericytes. Especially the endothelial cells restrict selectively the paracellular diffusion of macromolecules and polar solutes, which is due to the sealing function of the tight junctions (TJs). TJs are mainly composed of three classes of transmembrane proteins including the claudin family. Up to now, the claudin family consists of 27 members showing a tissue-specific expression pattern. Especially, claudin-5 is known to be a key TJ protein tightening the BBB for molecules up to 800 Da. Therefore, claudin-5 is a promising target for the size-selective opening of the BBB, which is especially necessary in the treatment of CNS disorders.Those disorders account for about 11 % of the diseases and 1 % of the deaths worldwide and are currently treated inadequately. For this reason, drug enhancer peptides derived from the claudin-5 sequence were designed to modulate claudin-5 and thereby permeabilize the BBB for small drug molecules transiently.he increased permeability will be validated by in vivo assessment of different size markers at different time points after application of the enhancer peptidomimetics.

Furthermore, the in vivo tolerance is assessed and the peptidomimetics will be optimized and characterized in cell culture assays by using primary and immortalized endothelial cell lines. So far, the cell culture models and the in vivo permeability assays are established. First results indicate an opening of the blood-brain barrier for small molecules after treatment with the peptidomimetics.

11 MODELING HIPPOCAMPAL RIPPLES IN-VITRO: INTRA-RIPPLE FREQUENCY DYNAMICS AND RESPONSE TO PHARMACOLOGY

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Sharp wave-ripples (SWRs) are highly synchronous network events displayed by the mammalian hippocampus during slow-wave sleep and immobile resting periods. Such events are believed to be involved in memory consolidation. A SWR is characterized by fast network oscillations (~ 200 Hz "ripples") superimposed by a slow sharp wave (< 50 Hz). Ripples are characterized by intra-ripple frequency accommodation (IFA): A steady ripple frequency on the first half of the event is followed by a prominent deceleration of frequency on the second half [1]. In vitro, the ripple frequency is insensitive to changes of GABAA receptor peak-conductance and decay time-constant [2]. Both features constrain the class of models that can explain SWRs. Two generative mechanisms have been proposed as the origin of the high-frequency component: First, an interneuron network coupled by chemical synapses that self-entrain to the ripple frequency. Second, a rhythmic output of a network of electrically coupled axons of pyramidal cells. The robustness of the 200-Hz ripple frequency to pharmacological manipulation of GABAA receptor parameters has been interpreted as evidence against an interneuron-based pacemaking mechanism [2]. Here we analyze a physiologically constrained computational model of an interneuron-network that exhibits several features of hippocampal SWR both in its time-course and in its pharmacological profile. If the network is in the regime of "sparsely synchronized" oscillations [3], the ripple frequency is insensitive to changes of GABAA receptor peak-conductance and decay time-constant. Additionally, when the network is driven by an excitatory burst, its transient response exhibits IFA, which can be explained by interactions between excitatory and inhibitory currents in each ripple cycle. Finally, we suggest new experiments that allow to test the interneuron-network hypothesis for SWRs.

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12 TRANSCRIPTIONAL AND EPIGENETIC DYNAMICS DURING ES CELL DIFFERENTIATION IN TO DOPAMINERGIC NEURONS

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Embryonic differentiation starts from a totipotent cell and culminates with the production of all the specialized cells in the higher organisms but how this is orchestrated is still not well understood. Our lab has previously shown that an important cohort of developmental regulator genes are kept in a poised conformation in ESCs (Stock et al. 2007, Brookes et al. 2012). The poised state is found in 30% of all genes in ES cells, is characterized by an association with Polycomb repressor complexes and an unusual form of RNAPII phosphorylated on Ser5 which elongates through coding regions in the absence of Ser2 and Ser7 phosphorylation. It remains unknown whether the poised state of RNAPII at Polycomb-repressed genes is a property of ESCs or such regulation is present and plays a role in lineage commitment, such as in neuronal differentiation. We have used high-throughput approaches to examine the changes in gene expression and RNAPII poising during the early and late differentiation of mouse ESCs into Dopaminergic Neurons. We have generated in-depth maps of transcriptomes, a panel of RNAPII posttranslational modifications and Polycomb histone modification.Our study provides a global view of the dynamic RNAPII modification changes across the genome that accompany Neuronal differentiation in the dopaminergic lineage specification and the contribution played by Polycomb in such process. The integration of the data obtained provides important insights about the regulatory networks that exist in ES cells to maintain developmental regulator genes in a poised conformation, and how dynamically these networks change during neuronal differentiation.

13 THE D2 RECEPTOR PARTIAL AGONIST 2-BROMOTERGURIDE DOES NOT AFFECT BODY WEIGHT AND BODY FAT COMPOSITION OF RATS

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Introduction: Schizophrenia is a chronic psychiatric disorder. Current antipsychotic therapy has limited efficacy and association with severe side effects, e.g. motor adverse effects, weight gain and changes in body fat composition. Dopamine D2 receptor partial agonists represent a sophisticated option for effective antipsychotic treatment with diminished adverse effects. Our previous in vitro and in vivo data revealed that the terguride derivative 2-bromoterguride (2-BT) is a partial agonist at dopamine D2 receptors with promising antipsychotic characteristics.Methods: Here, chronic effects of 2-BT (0.1 and 0.3 mg/kg for 21 days; twice daily) on food and water intake, body weight and fat tissues were examined in female Sprague Dawley rats with the same doses as used before. Additionally, we investigated the influence of chronic 2-BT on spontaneous behaviour in the open field box and cataleptic behaviour in the bar and grid test. The positive control was the atypical antipsychotic olanzapine (2 mg/kg).Results: In contrast to olanzapine, chronic 2-BT administration did not induce changes in food and water intake, body weight and body fat composition compared to vehicle group. Similar to acute conditions, 2-BT brought on no cataleptic behaviour but decreased spontaneous locomotion. Conclusions: Apparently, 2-BT possesses no liability to weight gain and does not change body fat composition. Both doses of 2-BT seem to be slightly sedative without inducing motor adverse effects. The present study confirms our previous observations that the D2 receptor partial agonist 2-BT may be a promising candidate for the treatment of schizophrenia with minor adverse effects.

14 CHARACTERIZATION OF CELL-DEATH MECHANISMS WITHIN THE CENTRAL AUDITORY PATHWAY UPON REPEATED NOISE EXPOSURE

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A single noise trauma induces apoptosis within the central auditory pathway.

It is of highly interest if a repeated noise trauma elicit additional cell death cascades in a pre-damaged central auditory pathway. Mice under anesthesia were sound exposed (5-20 kHz, 115dB SPL for 3h) an investigated two weeks after the first trauma. Some of them were, 7 days after the first trauma, exposed to the same trauma a second time ("Double-Group") while the other animals stayed in there cages ("Single-Group"). The animals´ brains were cut in 10µm slices and TUNEL-stained (Terminal deoxynucleotidyl transferase dUTP nick end-labeling) to visualize Cell-Death mechanisms. TUNEL positive cells were counted manually in standardized grids in the ventral and dorsal cochlear nucleus (VCN and DCN), in the central part of the Inferior Colliculus (ICC), in the dorsal, ventral and medial subdivisions of the medial geniculate body (dMGB, vMGB and mMGB), as well as in the 6 histological layers of the primary auditory Cortex (AI). Significant more TUNEL positive cells were detected in all subdivisions of the MGB as well as in the layer I and III of the AI of the Double-Group. There was no significant difference of TUNEL-positive cell density between the single-group and double-group in the basal structures (VCN, DCN and ICC) and in the other layers of the AI.These results underline the influence of a second noise trauma on the central auditory pathway that we could recently show (Gröschel et al 2011). A second noise trauma seems to affect mainly the higher auditory structures since the lower auditory pathway is already adapted to the post-traumatic cochlear pathology.

15 EMOTIONAL STATES AND MEMORY-RELATED EEG OSCILLATIONS

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It is well established that the emotional state (ES) during information encoding strongly influences the way in which memories are formed. In two recent studies (Gärtner & Bajbouj 2014, Gärtner et al. 2014), we investigated effects of the ES on induced oscillatory EEG activity during information encoding in different memory tasks. In the first study, we show that the ES modulates encoding-related oscillations during an episodic memory task. While successful encoding in a positive ES was specifically accompanied by widespread synchronization in the delta (1 - 4 Hz) frequency range, encoding success in a negative ES was related to frontal desynchronization in the beta (15 – 25 Hz) range. We argue that widespread delta oscillations are related to the process of elaborative encoding,

which is promoted during a positive ES. Furthermore, we argue that the observed effect in the beta band is related to the activation of distinct, highly specialized cortical regions. Encoding in a negative ES has been linked to careful and accurate stimulus processing that might rely on the activation of such regions. In the second study, we show that a negative, stressful ES during a working memory (WM) task leads to power decreases in frontal theta (4 – 8 Hz) activity and to decreased WM performance. We relate this finding impaired prefrontal network connections and to difficulties in suppressing task-irrelevant thoughts. Despite the differences between the two mentioned studies, a common finding is that neural oscillations in slow frequency ranges (delta, theta) are suppressed in negative emotional states. Neural synchronization in these frequency bands has been linked to the integration of information of distinct cortical regions. Here, we would like to discuss the idea that positive ES promote such integration processes, while negative ES tend to suppress them.

16 JOINT REGULATION OF DEFENSIVE BEHAVIOR AND CIRCULATORY RESPONSES BY HYPOTHALAMIC CIRCUITS

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During defensive behaviors like freezing and flight characteristic repertoire of cardiovascular responses is associated with psychological stress. Yet operation of neural pathways which control hemodynamic responses is not well understood. Medial hypothalamic (MH) nuclei are involved in regulation of circulatory output according to metabolic and behavioral demands. In this study, we combined optogenetics with neuronal and electrocardiographic recordings in behaving mice to study the role of MH circuitry and of its afferents in cardiovascular responses to aversive stimuli. We locally expressed an excitatory opsin ChETA in GABAergic cells in VGAT-Cre mouse line and performed continuous monitoring of heart rate, neuronal activity and behaviour during optostimulation in MH. Optostimulation resulted in frequency- and duration- dependent changes in heart rate and its variability. These effects were accompanied by expression of defensive behavioural patterns. We further analyzed functional readout of MH neurons and neuronal activity fingerprints of the frontal lobe networks during defensive behavior and the physiological regulation of heart rhythm.

17 THE NAKED MOLE RAT AUDITORY BRAINSTEM: AN ANATOMICAL AND NEUROCHEMICAL DESCRIPTION

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The African naked mole rat (Heterocephalus glaber) uses a large vocal repertoire for communication yet displays high auditory thresholds (~40-50 dB) and poor performance in sound localization. Their hearing is also predominantly sensitive to low frequency sounds. Here, we addressed whether these poor hearing abilities are correlated with a rudimentary auditory anatomy using immunohistochemical procedures.Perfused brain sections of the auditory brainstem and midbrain were immunostained using antibodies raised against VGluT1, GlyT2, HCN1 and MAP2 to characterize both the synaptic inputs and the auditory structures. All the prominent nuclei of the auditory brainstem are present. The major subdivisions of the cochlear nucleus (CN) can be identified. In the superior olivary complex (SOC) the lateral superior olive (LSO) is large and elongated, in contrast to a small medial superior olive (MSO). The medial nucleus of the trapezoid body (MNTB) consists of only a low number of neurons scattered within the trapezoid body. Still, both LSO and MSO neurons receive prominent glycinergic inputs. In contrast, the ventral and dorsal nucleus of the lateral lemniscus (VNLL; DNLL) and the inferior colliculus are of comparable size to other rodents. Only VNLL but not LSO and MSO neurons display strong HCN1 immunolabelling. Despite their poor sound location abilities, these animals have a large LSO and a small MSO. HCN1 labeling, which is an indicator of temporally precise integration of synaptic inputs, is, unlike in other rodents, almost completely missing in the LSO and MSO. We speculate that this missing HCN1 labeling contributes to the sluggish sound localization abilities of these animals.

18 PANEL REGRESSION MODELING OF OPTOGENETIC INTERROGATION OF NETWORK OSCILLATIONS

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Assessment of optogenetic stimulation effects includes estimation of efficacy, determinism and replicability of the optical control over a target process.

This task is particularly relevant for complex read-out processes, like network oscillations, owing multifactorial relationships between activity of light-sensitive neurons and their contribution to population dynamics. Here we addressed this problem in data obtained in experiments with optogenetic stimulation (with ChR2 or ChETA) of parvalbumin (PV)-positive interneurons in parallel with recording of local field potential and neuronal discharge in behaving mice. In the first dataset, theta rhythm (5-10 Hz) was paced by excitation of septal inhibitory projections to hippocampus. In the second dataset, ripple oscillations (140-200 Hz) were manipulated by optostimulation of PV-positive cells in hippocampus. Panel regression model was used to investigate and quantify the effect of repeated laser stimulation on the network oscillation after adjustment for efficacy, dominance, determinism and temporal replicability of the optical control of the neuronal discharge. Non-parametric inferential methods were used to gain insight about data distributions and improve accuracy. Our analysis suggests that time-resolved quantification of optogenetic interventions is instrumental for studies of causal links between activity of individual neurons, collective network dynamics and behaviour.'

19 THE TPH2-KNOCKOUT RAT - PHYSIOLOGICAL AND BEHAVIORAL ANALYSIS OF A SEROTONIN DEFICIENT RAT MODEL

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Serotonin is a neurotransmitter in the central nervous system, which is discussed to play a role in the etiology of depression, phobias, and other psychiatric dysfunctions. To investigate the influence of central serotonin deficiency on cognition and affection we previously used a mouse model with a genetic deletion of Tryptophan hydroxylase 2 (TPH2), the rate limiting enzyme of serotonin-synthesis in the brain. In mice the TPH2-deletion is correlated with a hyperaggressive behavior, combined with a loss of aversive behavior. The results for other behavioral assays, such as tail-suspension and forced swim test, which allow the evaluation of depression-like phenotypes remained more controversial and hence call for an alternative animal model. For this purpose, we generated Tph2-/- rats via a zinc-finger-nuclease (ZFN) based gene-deletion.' The rat is the preferred animal model for the analysis of cardiovascular and behavioral phenotypes and results in this species can be more reliably transferred to the human situation than mouse data. Rats with TPH2-deletion showed no detectable serotonin in the brain. Tph2-/- rats appeared anyhow to be vital and gave birth to healthy offspring, although during their first postnatal weeks TPH2 knockout rats exhibit growth retardation, similar to the mouse-model. We tested hedonic behavior and analyzed cardiovascular and behavioral parameters in different stress-situations, i.e. handling, mating, open field test and positive conditioning. Furthermore, we examined the behavioral response and neurogenesis of Tph2-/- males to a chronic positive conditioning in the tickling paradigm. Altogether we could provide a broad behavioral and physiological phenotyping of the first rat model lacking serotonin in the brain.

20 CALCIUM-RELATED ACTIVITY IN THE CENTRAL AUDITORY SYSTEM AFTER AGE-RELATED OR NOISE-INDUCED HEARING LOSS

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Beside changes in the periphery, hearing loss is followed by several pathologies in the central auditory system. It remains unclear how far the observed effects differ in relation to the cause of hearing loss. It was the aim of this study to compare the time-dependent changes in calcium-dependent neuronal activity in mice with age-related or noise-induced hearing loss. One group of mice (NMRI strain) was exposed to traumatizing broadband noise (5-20 kHz at 115 dB SPL for 3 hours). Another group consisted of old animals showing age-related hearing loss. Auditory threshold shifts were determined by ABR recordings. Calcium-dependent neuronal activity was measured by 7T-MRI scanning 24 hours after injection of a manganese chloride solution. Hearing loss and MRI signal strengths in central auditory structures were measured at different points in time and compared to normal hearing controls. The ABR recordings demonstrate a significant threshold shift in the experimental groups compared to normal hearing animals. The level of hearing loss is independent of the time of investigation within the groups. Animals with age-related and noise-induced hearing loss show an increase in manganese accumulation in several structures compared to controls in the earlier measurements,

which is followed by a subsequent decline at the later points in time. The data indicate that hearing loss has large effects on calcium-dependent activity in central auditory structures. Although auditory threshold shift seems to be persistent over the investigated period, calcium-dependent neuronal activity is increased over a specific period in both noise-induced and age-related hearing loss and decreases afterwards. These effects could be explained by the appearance of hyperactivity and especially neuroplasticity early after the onset of threshold shift, whereby these processes are partly reduced in case of a permanent, long-lasting hearing loss.

21 THE ROLE OF SEROTONIN IN RUNNING-INDUCED NEURONAL ACTIVITY

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Serotonin (5-hydroxytryptamine) is a small biogenic amine with functions in the peripheral as well as the central nervous system (CNS). As neurotransmitter, serotonin was recently shown to be necessary for the running-induced increase in adult neurogenesis, the generation of new neurons in the dentate gyrus (DG). The mechanisms coupling physical activity with neuron formation via serotonin are not yet fully understood. This project aims at investigating brain areas that are affected by serotonin signaling during exercise. Mice lacking the enzyme TPH2 with central serotonin deficiency (TPH2 -/- mice) have been generated in the Bader lab and serve as an effective tool for this study. Analysis was done with TPH2 -/- mice in comparison to serotonin competent (TPH2 +/+) animals. Methods used in my study comprise 20 min sessions of forced running on a rodent treadmill. Neuronal firing was detected by labeling expression of the immediate early gene c-Fos on histological brain slices. Surprisingly, no changes in c-Fos expression have been observed in serotonergic neurons of the brain stem raphe nuclei. However, quantification of c-Fos expression in the DG revealed a significant increase in activated neurons in TPH2 +/+ as well as TPH2 -/- animals after running. These data show a condition rather than a genotype effect. Thus, the observed result seems to be serotonin independent and other neurotransmitters may mediate running-induced cell activation in the DG. Further analysis will be done for other brain regions.Studying intracellular signaling mechanisms is of great clinical importance for the development of novel therapeutic approaches.

22 FREE RADICAL DEPENDENT NEUROVASCULAR DE-COUPLING IN AN IN VITRO MODEL OF STATUS EPILEPTICUS

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Metabolic dysfunction, deregulation of neurovascular coupling and blood brain barrier (BBB) break down are common events in epilepsy and might contribute to the progression of the disease. Formation of oxygen and nitrogen centered free radicals was described in different epilepsy models, but their role in BBB-breakdown and the de-coupling of the neurovascular unit in epilepsy are less understood. Here we report on a slice culture-based model for studying neurovascular coupling and BBB function during epileptiform activity. Slice cultures retain an elaborated network of vessels, whose lumen is segregated from the interstitium by a diffusion barrier related to BBB. Vasoconstriction was induced by mechanical stimulation of the pericytes, increased intraluminal pressure and thromboxane, whereas nitric oxide induced dilatation of pre-constricted vessels. Oxidative metabolism was enhanced during seizure-like events (SLE) as revealed by monitoring tissue pO2 and NAD(P)H redox ratio. Nevertheless, following a short oxidative shift, NAD(P)H become reduced during the whole duration of a SLE. Overly reduced electron transport chain complexes in presence of high mitochondrial [Ca2+] might facilitate mitochondrial superoxide formation and hydrogen peroxide release. Pre-constricted vessels dilated following the onset SLEs indicating functional neurovascular coupling in slice cultures. However, SLE-associated vasodilatation became smaller during the course of recurrent SLEs. Remarkably, free radical formation was also enhanced in pericytes and the oxidative stress led to vasoconstriction in naïve vessels and loss of SLE-dependent vasodilatation in pre-constricted vessels. The free radical scavenger TEMPO could partially prevent vasoconstriction. Occasionally, disruption of BBB occurred during vasoconstriction leading to loss of intraluminaly accumulated fluorescent probes. In conclusion, epileptiform activity dependent free radical formation might be sufficient to disturb neurovascular coupling and increase permeability of BBB.

23 EFFECTS OF BLOOD-BRAIN BARRIER DYSFUNCTION ON RESPONSE TO ANTIEPILEPTIC DRUGS IN THE HIPPOCAMPUS

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Hypothesis: Pharmacoresistance is affecting 30 % of epileptic patients and the ratio increases in focal and partial epilepsies. Recent studies indicate that blood-brain barrer dysfunction is common among patients with pharmacoresistant epilepsy. We hypothesized that the presence of interstitial albumin, the most abundant protein in serum, may contribute to pharmacoresistance either by buffering of the antiepileptic drugs or by leading to transcriptional changes that may in turn affect the drug efficacy. Methods: Seizure-like events were induced by 4-Aminopyridine in acute rodent entorhinal cortex-hippocampus slices. Extracellular field potential recordings were performed in entorhinal cortex layer III/IV in order to evaluate the effects of the standard antiepileptic drugs (phenytoin, valproic acid, carbamazepine and phenobarbital) in the presence of acute albumin or 24 hrs after its application. Unbound drug concentrations were quantified by ultrafiltration and high-pressure liquid chromatograpy. Results: Antiepileptic drugs failed to suppress seizure-like events in the presence of albumin. This effect was not seen in rodents that were pretreated with albumin 24 hrs before the experiments suggesting the acute buffering effect of albumin on antiepileptic drugs. Conclusions: A dysfunctional blood-brain barrier with acute extravasation of albumin could contribute to pharmacoresistance. The choice of an antiepileptic drug with low albumin-binding affinity may help in seizure control.

24 ABNORMAL CENTROSOME AND SPINDLE MORPHOLOGY IN HUMAN CELLS FROM PATIENTS WITH AUTOSOMAL RECESSIVE PRIMARY MICROCEPHALY SUBTYPES

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Primary autosomal recessive microcephaly (MCPH) is a rare neurodevelopmental disorder that results in severe microcephaly at birth with pronounced reduction in brain volume, particularly of the neocortex, simplified cortical gyration, and intellectual disability. Genes causing MCPH code for proteins implicated in regulation of centriole replication, centrosomal microtubule nucleation, organization of the mitotic spindle pole, cell-cycle checkpoint regulation and DNA damage response.' Despite considerable interest in MCPH, the underlying pathomechanisms resulting in the microcephaly phenotype have not been definitely established. Here we describe patients with primary autosomal recessive microcephaly types 2 and 3 (MCPH2 and MCPH3) caused by mutations in the WDR62 and the CDK5RAP2 genes, respectively. The patients revealed brain malformations including hypoplasia of the corpus callosum, simplified hippocampal gyration, widened lateral sulci, and cerebellar hypoplasia with an enlarged cisterna magna in addition to microcephaly. Further we investigated the cellular phenotype in MCPH2 and MCPH3 patient-derived lymphoblastoid cells and detected mitotic spindle defects and centrosomal integrity defects as a shared pathogenic phenotype in both MCPH2 and MCPH3 patients. As a conclusion, based on the cellular phenotype observed, we propose that a disruption of centrosome integrity and/or spindle organization play an important role in the development of microcephaly in MCPH2 and MCPH3.

25 NEURON-ASTROCYTE INTERACTIONS CONTRIBUTE TO CHANGES IN PLASTICITY IN THE HIPPOCAMPUS IN AN ANIMAL MODEL OF POSTTRAUMATIC STRESS DISORDER

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Psychological stress is associated with the development of a variety of psychiatric diseases. For posttraumatic stress disorder (PTSD), traumatic experiences are by definition required as an underlying factor of the symptoms. It was suggested that aversive childhood experiences are a risk factor for the development of PTSD. Therefore, we used a rat model for PTSD which comprises a composite juvenile stress (JS; P27-29) and an adult stress (AS; P60-80). Recent studies demonstrate an important role of glial-neuronal interactions in synaptic plasticity and learning. Astrocytes are involved in uptake and synthesis of neurotransmitters such as glutamate and GABA, next to regulation of ion homeostasis and energy supply (Halassa & Haydon, Annu Rev Physiol, 2010). Taken together, interactions between astrocytes and neurons appear to be well suited for chronic modifications following experience of extreme stress, contributing to the development of PTSD-related symptoms.

In the current project we first targeted the role of the astrocytic enzyme glutamine synthetase (GS) in long term potentiation in the CA1 region of the ventral hippocampus. Antagonizing GS with methionine sulfoximie led to a significant increase of LTP. First evidence suggested a compromised glutamine supply as an underlying mechanism of this effect. In both JS and JS/AS treated animals, MSO did not alter LTP, indicating reduced GS-activity. This finding was supported by a reduced expression of GS in JS-animals. Moreover, we found long-term expression changes of further key astrocytic proteins also in the dentate gyrus, which suggests a widespread effect of psychological stress on astrocytic-neuronal interaction within the hippocampus.

26 DEFICIENCIES IN FOLIC ACID AND UNG RESULT IN LEARNING DEFICITS, AND DECREASED MMP-9 LEVELS IN A MOUSE MODEL OF VASCULAR DEMENTIA

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Dietary deficiencies in folic acid result in elevated levels of plasma homocysteine. Recently, epidemiological studies have associated elevated levels of plasma homocysteine with the development of dementia, however the pathophysiology remains unclear. Additionally, uracil-DNA glycosylase (UNG) is involved in DNA repair and previous work has linked folate deficiency in UNG-/- mice to neurodegeneration. The purpose of this study is to evaluate how deficiencies in folic acid and DNA repair affect the progression vascular dementia using an animal model of chronic cerebral hypoperfusion. Wild-type and knockout UNG mice were placed on either control (CD) or folate deficient (FADD) diets. Six weeks later, the mice underwent implantation of microcoils around both common carotid arteries or a sham procedure. Behavioural analysis began after 4-weeks and angiography was measured 5-weeks using MRI. At 6 weeks, plasma homocysteine levels were measured and RNA, and proteins were isolated from cortical tissue. Interestingly, FADD wild-type sham and microcoil mice displayed remodelling of the basilar artery and vasculature at the base of the brain. All FADD mice had significantly higher plasma homocysteine levels when compared to CD mice. Changes in short-term memory of UNG-/- microcoil mice were observed in the y-maze. Furthermore, FADD UNG-/- microcoil mice exhibited learning impairments in the MWM. Cortical MMP-9 protein levels were increased in all FADD wild-type mice and decreased in FADD UNG-/- microcoil animals. CD and FADD UNG-/- microcoil mice had increased cortical mRNA expression of IQSEC1. Our results suggest that a deficiency in folic acid and UNG in combination with chronic hypoperfusion significantly impairs spatial learning in UNG-/- mice. This behavioural change may be a result of decreased in gene expression of IQSEC1, a signalling molecule involved in learning and memory and changes in protein levels of MMP-9. (Supported by FRSQ, CANADA)

27 NOVEL COMPOUNDS TARGETING MICROGLIAL ACTIVATION

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Microglia, the resident macrophages of the brain, actively survey the CNS tissue for any changes in the brain homeostasis. Upon an inflammatory stimulus, they respond with a reaction, also known as microglial activation, characterized by amoeboid morphology, phagocytic activity and release of pro-inflammatory cytokines, reactive oxygen species and nitric oxide. These can have detrimental effect on neurons and can increase brain damage, for example in demyelinating disorders like multiple sclerosis or in Alzheimer's disease. Thus, it is of therapeutic interest to find new molecules, which are capable of specifically inhibiting microglial activation. We tested 30000 chemical compounds for their ability to reduce lipopolysaccharide (LPS)-induced nitric oxide (NO) release in the BV2 microglial cell line, measured by the Griess assay using the high throughput screening platform at the Leibniz-Institut für Molekulare Pharmakologie. We identified four compounds which significantly reduced NO release without being cytotoxic, and which matched certain biochemical criteria. The impact on NO release by these compounds was validated on primary cultured neonatal microglial cells. We also tested whether these compounds could inhibit the LPS induced release of the cytokines TNFα, IL1β, IL6. Two of the compounds decreased the cytokine release in a dose dependant manner, however, did not entirely block it. One compound did not affect the cytokine release at all, a second led to a dose-dependent increase of the tested cytokines.

Thus, we identified two novel compounds which specifically inhibit microglial activation and further studies will elucidate their therapeutic potential in inflammatory diseases.

28 MINERALOCORTICOID RECEPTOR STIMULATION IMPROVES COGNITIVE FUNCTION AND DECREASES CORTISOL SECRETION IN DEPRESSED PATIENTS AND HEALTHY INDIVIDUALS

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Background: People with major depression often show impaired memory and executive function as well as increased cortisol secretion. Being predominantly expressed in the hippocampus and in the prefrontal cortex, mineralocorticoid receptors (MR) are linked to memory function and cortisol secretion. Therefore we investigated whether specific fludrocortisone-induced stimulation of MR 1) improves memory and executive function and 2) decreases cortisol levels in participants with major depression and healthy controls. Methods: In this randomized, double-blind, within-subject cross-over study design, twenty-four unmedicated depressed patients and twenty-four age-, sex- and education matched healthy controls were treated with either 0,4 mg fludrocortisone or placebo. Memory and executive functions were assessed between 14:00 and 17:00 hours, cortisol secretion was measured during cognitive testing using saliva samples. Results: 1) Fludrocortisone-induced stimulation of MR improved verbal memory and executive function across groups. In executive function and in psychomotor speed tests, people with major depression obtained worse results than their healthy counterparts. 2) Fludrocortisone-induced stimulation of MR decresed cortisol secretion across groups. We found a significant correlation between cortisol inhibition and verbal memory performance. In conclusion, MR stimulation reveals a possibility to improve cognitive function in depressed and in healthy participants.

29 CDK5RAP2 KNOCKDOWN IN MURINE EMBRYONIC STEM CELLS AFFECTS PROLIFERATION AND NEURAL DIFFERENTIATION, BUT NOT NON-NEURAL DIFFERENTIATION INTO BEATING CARDIOMYOCYTES

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Homozygous mutations in the Cyclin-dependent kinase 5 regulatory subunit-associated protein 2 gene CDK5RAP2 lead to autosomal recessive primary microcephaly type 3 (MCPH3), a neurodevelopmental disorder characterized by an isolated defect of the brain. Patients with MCPH develop severe microcephaly in utero, affecting particularly the neocortex and are mentally retarded. The centrosomal protein CDK5RAP2 plays a role in centrosome function, spindle formation and dynamics, spindle checkpoint control and DNA damage response. While the exact pathomechanism leading to the MCPH phenotype still has to be elucidated, the current model invokes a premature shift from symmetric to asymmetric neural progenitor-cell divisions with a subsequent depletion of the progenitor pool. To investigate, why an isolated neural phenotype occurs despite ubiquitous expression of the centrosomal CDK5RAP2, we analyzed neural and non-neural differentiation of Cdk5rap2-depleted murine embryonic stem cells. We demonstrate an accumulating proliferation defect of neurally differentiating stem cells and cell death of proliferative and early postmitotic cells. Moreover, we show that non-neural differentiation into beating cardiomyocytes is not affected by Cdk5rap2 knockdown. Our data underline that MCPH is caused by defective proliferation and cell-fate determination of neural progenitors during neurogenesis.

30 CDK5RAP2 KNOCKDOWN IN MURINE EMBRYONIC STEM CELLS AFFECTS PROLIFERATION AND NEURAL DIFFERENTIATION, BUT NOT NON-NEURAL DIFFERENTIATION INTO BEATING CARDIOMYOCYTES

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The mineralocorticoid receptor (MR) is highly expressed in the hippocampus and prefrontal cortex. MR play an important role in appraisal processes and in modulating stress-associated emotional reactions but it is not known whether the MR affects empathy. Borderline personality disorder (BPD) is characterized by disturbed emotion regulation and alterations in empathy.

In the current study, we examined whether stimulation of the MR enhances empathy in patients with BPD and healthy individuals. In a placebo-controlled study, we randomized 38 women with BPD without psychotropic medication and 35 healthy women to either placebo or 0.4 mg fludrocortisone, a MR agonist. Subsequently, all participants underwent two tests of social cognition, the Multifaceted Empathy Test (MET) and the Movie for the Assessment of Social Cognition (MASC), measuring cognitive and emotional facets of empathy. Eighteen BPD patients and 18 healthy women received placebo, while 20 BPD patients and 17 healthy women received fludrocortisone. In the MET, fludrocortisone enhanced emotional empathy across groups while cognitive empathy was not affected. In the MASC, no effect of fludrocortisone could be revealed. In both tests, BPD patients and healthy women did not differ significantly in cognitive and emotional empathy and in their response to fludrocortisone. Stimulation of MR enhanced emotional empathy in healthy women and in BPD patients. Whether fludrocortisone might play a therapeutic role in psychotherapeutic processes, remains to be elucidated.

31 NOVEL FUNCTIONS OF C-JUN N-TERMINAL KINASES IN NEURONS

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The c-Jun N-terminal kinases (JNKs) are stress-activated serine-threonine kinases that have recently been linked to various neurological disorders. In patients with intellectual disability (ID), we detected de novo truncations in the CNS-expressed MAPK10/JNK3 gene, highlighting an important role for JNK3 in human brain development. To further elucidate the function of JNK3 in the brain, we searched for neuronal interaction partners and novel phosphorylation targets. We identified several novel JNK3 interaction partners, including synaptic membrane-associated guanylate kinase (MAGUK) PDZ-domain proteins (involved in ID) and the Shank proteins (involved in autism), as well as CRMP1 and GPRIN family proteins. We are currently investigating the molecular properties of these interactions, focussing in particular on MAGUK family of JNK binding partners. Using phospho-specific antibodies, we are investigating the influence of JNK-mediated phosphorylation on the subcellular localisation of selected endogenous post-synaptic scaffold proteins in hippocampal rat neurons. We will also use viral-mediated gene transfer of tagged phospho-mimicking / phospho-deficient expression constructs and subsequent FRAP experiments to explore how the mobility of these novel JNK targets is regulated. Given the location of JNK docking and phosphorylation of these post-synaptic scaffold proteins, specific protein-protein interactions and subsequent signalling may also be affected by JNK. We will investigate how JNK phosphorylation of MAGUK family proteins influences their binding to selected neuronal proteins, including e.g. Nedd4, which has been implicated in SAP102 mono-ubiquitination and microtubule-dependent protein trafficking. Our data on novel synaptic JNK targets, together with the fact that JNK3 has been implicated in neurodevelopmental disorders, provide the impetus for further studies on novel functions of JNK3 in neurons.

32 MITOCHONDRIAL AND BIOENERGETIC REMODELING WITHIN HUMAN PSC-DERIVED NEURAL PROGENITORS

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Human pluripotent stem cells (PSCs)-derived neuronal cells hold great promises for the study of brain disorders “in a dish”. Nonetheless, little is known about the mitochondrial and bioenergetic state of neuronal-committed cells. We previously demonstrated that upon the induction of PSCs the metabolism transits from oxidative phosphorylation (OXPHOS) to glycolysis (Prigione et al, Stem Cells, 2010). Here, we investigated the mitochondrial remodeling occurring during the neuronal differentiation of human PSCs. Human PSCs were differentiated into stable neural progenitor cells (NPCs), using a direct small molecule-based approach. Electron microscope studies showed the occurrence of mitochondrial maturation during neuronal induction. Accordingly, during NPC generation the extracellular acidification rate (ECAR), measured with Seahorse flux analyzer, drastically decreased, indicating that NPCs relied more on OXPHOS metabolism than PSCs. Indeed, upon introducing glucose onto glucose-starved cells, only PSCs- and not NPCs nor fibroblasts- showed a dramatic ECAR elevation coupled by a reduction of oxygen consumption rate (OCR), suggestive of preferential employment of glucose as a substrate for glycolysis rather than for OXPHOS. However, OCR levels within NPCs were not as high as the ones of fibroblasts.

This was confirmed by bioluminescent ATP quantification, which detected low ATP content within NPCs. The mitochondrial DNA copy number of NPCs, although increased upon NPC conversion, also did not reach the same level of that of fibroblasts, even if the proliferative rate of NPCs and fibroblasts appeared similar and significantly lower than that of PSCs. Taken together, the data suggest that multipotent NPCs may be less glycolysis-dependent than PSCs and overall low metabolically active. These findings may pave the way to the employment of this cellular system for the study of neurological diseases in which mitochondrial dysfunction is a known pathogenetic culprit.

33 MINOCYCLINE RESCUES DECREASE IN NEUROGENESIS, INCREASE IN MICROGLIA CYTOKINES AND DEFICITS IN SENSORIMOTOR GATING IN AN ANIMAL MODEL OF SCHIZOPHRENIA

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Adult neurogenesis in the hippocampus is impaired in schizophrenic patients and in an animal model of schizophrenia. Amongst a plethora of regulators, the immune system has been shown repeatedly to strongly modulate neurogenesis under physiological and pathological conditions. It is well accepted, that schizophrenic patients have an aberrant peripheral immune status, which is also reflected in the animal model. The microglia as the intrinsic immune competent cells of the brain have recently come into focus as possible therapeutic targets in schizophrenia. We here used a maternal immune stimulation rodent model of schizophrenia in which polyinosinic-polycytidilic acid (Poly I:C) was injected into pregnant rats to mimic an anti-viral immune response. We identified microglia IL-1β and TNF-α increase constituting the factors correlating best with decreases in net-neurogenesis and impairment in pre-pulse inhibition of a startle response in the Poly I:C model. Treatment with the antibiotic minocycline (3mg/kg/day) normalized microglial cytokine production in the hippocampus and rescued neurogenesis and behavior. We could also show that enhanced microglial TNF-α and IL-1β production in the hippocampus was accompanied by a decrease in the pro-proliferative TNFR2 receptor expression on neuronal progenitor cells, which could be attenuated by minocycline. These findings strongly support the idea to use anti-inflammatory drugs to target microglia activation as an adjunctive therapy in schizophrenic patients.

34 THYROID HORMONES INFLUENCE NEURONAL ENERGY METABOLISM VIA THYROID HORMONE TRANSPORTERS

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Thyroid hormones influence neuronal energy metabolism via thyroid hormone transporters. Thyroid hormones (TH) influence the energy metabolism throughout the whole body. They act on heat production and skeletal muscle development, increase oxygen consumption and ATP production. For their local action, TH needs to enter the cell via specific TH transmembrane transporters. Among them, the monocarboxylate transporter 8 (Mct8) has been identified as the most specific TH transporter. Mutations in MCT8 lead to a severe form of psychomotor retardation in combination with abnormal TSH, thyroxine (T4) and triiodothyronine (T3) level in humans, the Allan-Herndon-Dudley syndrome. Expression of Mct8 in neurons and astrocytes of the mouse suggested the syndrome to be caused by cellular TH deficiency in the brain. So far, nobody has analyzed the energy metabolism of brain cells in Mct8-deficiency. By using the Extracellular Flux Analyzer (Seahorse Bioscience, Massachusetts, US) and a defined serum-free self-made growth supplement, we were able to measure the oxygen consumption rate (OCR) under different TH conditions in primary cultures of Mct8-deficient neurons compared to cultures from wild type littermates. A five day treatment of wild type neurons with increasing concentrations of T3 and T4 (0, 3 and 10nM) leads to an increase in OCR. Mct8-deficient neurons respond similar to T3, while they show a lower basal respiration compared to controls. ATP production was not different between both groups in the presence of T3. However, treatment of Mct8-deficient neurons with T4 does not lead to a similar increase as in OCR of wild type neurons. ATP production is also hampered. This functional data indicates the presence of another TH transporter in Mct8-deficient neurons, which is capable of T3, but not T4 transport. We will further characterize the influence of TH transporters on energy metabolism in primary neuronal cultures using additional genetic and pharmacological models.

35 AMBIENT GLUTAMATE – A TOOL TO DISSECT SYNAPTIC AND EXTRASYNAPTIC NMDA RECEPTOR POPULATIONS IN ACUTE HIPPOCAMPAL SLICES OF THE RAT

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Aims: Depending on their subcellular localization, NMDA receptors (NMDARs) promote neuronal survival or death. Synaptic NMDARs are coupled to pro-survival signaling whereas extrasynaptic NMDARs (ES-NMDARs) activate pro-death pathways. The aim of the study was to quantify the number of ES-NMDARs in hippocampal CA1 pyramidal neurons. Methods: Whole-cell patch clamp recordings were made from CA1 hippocampal pyramidal neurons in brain slices prepared from Sprague Dawley rats of either sex (P35 - P42). NMDARs meditated EPSCs were elicited by 0.1 Hz stimulation of the Schaffel collaterals. Local puff applications of NMDA from a pipette attached to a picospritzer activated a local region of the dendritic NMDAR pool, containing both ES NMDARs and synaptic NMDARs.Results: We took advantage of the tonic activity of ES-NMDARs mediated by ambient glutamate whose spatial distribution is tightly regulated by the glutamate transporter. Ambient glutamate is thought to be excluded from the synaptic cleft and and thus preferentially interacts with ES-NMDAR. After the incubation of the slice with MK-801, a quasi-irreversible NMDAR open channel blocker, 75.3±2.8% of the EPSC amplitude remained unblocked in contrast to 53±3% of the puff response ($p < 0.005$).Conclusion: The stronger reduction of the puff mediated amplitude is consistent with the preferential activation of ES-NMDARs by ambient glutamate and subsequent block in the presence of MK-801. Ambient glutamate can serve as a tool to dissect extrasynaptic and synaptic NMDAR populations. Estimation derived from these experimental results suggests that at least one quarter of NMDARs in the apical dendrites are located extrasynaptically.

36 COMPARISON OF TWO METHODS TO DETERMINE RELATIVE FLAIR SIGNAL INTENSITIES OVER TIME IN ACUTE ISCHEMIC STROKE

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Background: For treatment of acute stroke patients, information on the time from symptom onset is essential. It is currently under debate, whether visibility of stroke lesions on MRI fluid attenuated inversion recovery (FLAIR) images can be reliably used as a marker for patients in the 4.5 h time window. Methods: We prospectively included patients that had an MRI examination within 4.5 h from symptom onset and received 2 to 5 MRI examinations on day 1 and 1 MRI examination on day 2. FLAIR relative signal intensities (rSI) were determined with two methods: with the software tool AnToNIa regions-of-interest (ROIs) on DWI were created, mirrored to the contralateral side and coregistered to FLAIR images. For the hotspot method an area of brightest signal on one slice of the FLAIR image and a corresponding contralateral spot were drawn. Proposed thresholds for the identification of patients within the time window are 1.15 for AnToNIa and 1.07 for the hotspot method. Results: We included 21 patients (6 female, median age 69 years, median NIHSS 5). FLAIR rSI determined with the hotspot were higher and more variable compared to the AnToNIa method. For the AnToNIa method only 1.7% and for the hotspot method 8.3% of the measurements done outside the time window were smaller than the proposed threshold. Conclusion: Results of the hotspot method strongly depend on the exact positioning of the ROI. Both methods seem reliable for excluding patients with time from onset of more than 4.5 h.

37 STUDYING REGENERATION OF THE CORTICOSPINAL TRACT IN ORGANOTYPIC SLICE CULTURES

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Studies of axonal repair after spinal cord injury are hampered by the complexity of the events involved. Here we present an improved, easy in vitro approach to investigate regeneration of the corticospinal tract and intrinsic parenchymal responses by preparing organotypic slice co-cultures. We used motor cortex of postnatal donor mice ubiquitously expressing green fluorescent protein and cervical spinal cord from coeval wild type pups. Our data show that a) motocortical outgrowth is already detectable after one day in culture and source specific; b) treatment with Neurotrophin-3 and C3 transferase from Clostridium botulinum significantly enhances axonal sprouting during the course of cultivation;

c) outgrowing axons form synaptic connections demonstrated by immunohistochemistry and calcium imaging; and d) all migrating cells of motocortical origin can be reliably identified without previous tracings and are mostly neural precursors that survive and mature in the spinal cord parenchyma. Thus our model is suitable to screen for candidate substance enhancing regeneration of the corticospinal tract and to study the role of endogenous neural precursors after lesion.

38 REGULATION OF PSD-95 COMPLEX ASSEMBLY

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The postsynaptic scaffold protein PSD-95 is an essential regulator of synaptic protein networks and synaptic transmission. We are interested in the molecular mechanisms by which PSD-95 proteins assemble and disassemble multiprotein complexes and thereby regulate synaptic plasticity. For this purpose we have developed a cell-based assay that takes advantage of established ligand / PDZ domain interactions for investigating scaffold protein complex formation. This assay allows for quantitative analysis of PDZ domain mediated protein clustering using bimolecular fluorescence complementation (BiFC): Two non-fluorescent fragments of a fluorescent protein (EYFP) are fused to C-terminal PDZ ligand sequences to generate split-EYFP probes that sense for PDZ domain binding grooves of adjacent (interacting) scaffold proteins. When these probes are brought into proximity by sequence-specific interaction with the PDZ domains of a multiprotein scaffold, a functional fluorescent EYFP molecule refolds and can easily be detected. We have used this system to examine the properties of PSD-95 variants and thereby delineated regions of importance for PSD-95 multimerization. Further analysis suggested that PSD-95 multimerization can be triggered by the binding of monomeric PDZ ligands to PSD-95 PDZ domains, suggesting that PDZ-ligand interactions may influence multiple aspects of PSD-95-mediated multiprotein complex formation. Thus our study provides a basis for future investigations into the nature of ligand-mediated PSD-95 multimerization in post-synaptic receptor clustering.

39 PREDICTIVE CODING FAILURE EXPLAINS AUDITORY GATING AND MISMATCH NEGATIVITY DEFICITS IN SCHIZOPHRENIA

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Background: The predictive coding model is rapidly gaining attention in schizophrenia research. Predictive coding posits the neuronal computation of residual variance ('prediction error') between sensory information and top-down expectation through multiple hierarchical levels. Event-related potentials (ERP) reflect cortical processing stages that are increasingly interpreted in the light of the predictive coding hypothesis. The mismatch negativity (MMN) is considered a direct prediction error correlate, while auditory gating is thought to be based on the absence of a prediction error signal. Methods: Twenty-five schizophrenia patients and 25 healthy controls underwent testing with two auditory tasks designed to elicit MMN and ERP gating responses. Auditory MMN and ERP gating were investigated using repeated measures models and strong spatiotemporal a priori hypotheses based on previous research. Separate correlations were performed for controls and schizophrenia patients. Results: MMN and auditory gating deficits were replicated in our sample of schizophrenia patients. Moreover, MMN and auditory gating measures were strongly anti-correlated in healthy controls, while no correlation was found in schizophrenia patients. Conclusions: This study provides evidence that auditory ERP components relevant for schizophrenia research can be reconciled in the light of the predictive coding framework. The lack of any correlation between the investigated measures in schizophrenia patients suggests a disruption of predictive coding mechanisms in general. More specifically, these results strongly suggest that schizophrenia is associated with an irregular computation of residual variance between sensory input and top-down models, i.e. prediction error.

40 THE EFFECTS OF COMPROMISED BLOOD-BRAIN BARRIER ON PLASTICITY CHANGES AND RESPONSE TO ANTIEPILEPTIC DRUGS IN THE HIPPOCAMPUS

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Dysfunction of the blood-brain barrier (BBB) has been shown to play a role, at least in part, in epileptogenesis following brain insult via leakage of serum albumin and transforming growth factor beta (TGFβ) signaling (Ivens et al., 2007). Expressional changes after activation of TGFβ signalling pathway was shown to include genes associated with immune response, excitatory and inhibitory neurotransmission and glial proteins which in turn suggested to be related with alterations of the network excitability in the brain (Cacheaux et al., 2009). The goals of our study are: (1) to evaluate the effect of brain exposure to serum albumin on homo- and heterosynaptic plasticity in the hippocampal network, (2) to observe possible changes in response to various antiepileptic treatments. As a model of compromised blood-brain barrier, acute brain slices from male Wistar rats were preincubated in artificial serum before recordings. Alternatively, artificial serum was applied intraventricularly at various time points before slicing. Various stimulation protocols were applied and extracellular field potentials were measured from different areas in the hippocampal network along with potassium concentration changes. Seizure like events (SLEs) were induced by 4-AP followed by application of standard antiepileptic drugs (AEDs) (Wahab et al., 2011) Both in preincubated slices and in slices from operated rats, network hyperexcitability was prominent both in baseline recordings and also recordings following various stimulation protocols. The affected tissue showed differential responses to AEDs.

41 HYPEROXIA IMPAIRS POSTNATAL GRANULE CELL DEVELOPMENT IN THE CEREBELLUM

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Preterm infants often suffer from neurological deficits caused by impaired postnatal brain development. Due to recent insights, pathologies of the cerebellum can be found in many former preterm infants, too, although causes are unclear. In general, damage of the developing brain has been related to perinatal inflammation/infection, hypoxia and hyperoxia. We aimed to investigate whether proliferation and maturation of cerebellar granule cell (GC) precursors are perturbed by postnatal oxygen toxicity. We used a hyperoxia model exposing newborn rats to 80% O2 for 24h from P6 to P7. Gene expression of markers of proliferation and neuronal maturation was analyzed by Real Time qPCR. Immunohistochemistry with antibodies against Ki67 and Pax6 was performed to analyze proliferation of GC precursors in the external granule cell layer. MRI was used in young adult rats at P30 to measure cerebellar volumes. As a result, hyperoxic rat pups had a significant downregulation of Shh and Ccnd2. Numbers of immature proliferating GCs colabeled with Pax6 and Ki67 were decreased after hyperoxia at P7. After recovery in room air, gene expression levels of Pax6, Tbr2 and Prox1 were lower in hyperoxia experienced rats at P11 and also at juvenile age P30. Cerebellar volume at P30 was significantly reduced after postnatal hyperoxia compared to control litters.In our study in rats, postnatal hyperoxia perturbed GC development. As a conclusion, maldevelopment of the cerebellum found in preterm infants could be caused by postnatal oxygen toxicity.

42 CORRELATION OF FLORBETABEN AMYLOID PET IMAGING AND THE AMYLOID PEPTIDE Aß42 IN THE CEREBROSPINAL FLUID

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Amyloid beta (Aß) peptides are the main component of amyloid plaques present in the Alzheimer´s disease (AD) brain. For this reason compounds which can be used in positron emission tomography (PET) to directly visualize Aß plaques have come into focus as a tool to improve diagnosis of AD. This study addresses the question how cerebrospinal fluid (CSF) levels of the Aß42 peptide correlate to PET signals using the tracer Florbetaben. Aß42 peptide concentrations in CSF were quantified using electroluminescence linked immuoassays. PET data were obtained from 45 patients (38 AD patients, 7 healthy controls). To quantify PET data, neocortical tracer uptake patterns were evaluated 90–110 min post-injection. PET images were assessed quantitatively to generate standard uptake value ratios (SUVRs), taking the cerebellar cortex as the reference region. To assess the relation between SUVR values in different brain regions and Aß42 concentration in CSF, correlation coefficients were calculated. We found overall negative correlations that highlight the coincidence of low Aß42 levels and high SUVRs.

Also the composite SUVR, calculated from six different cortical brain regions exhibits a strong correlation to Aß42 CSF level. We thus conclude that the 18F-labelled amyloid tracer Florbetaben signal strength correlates to CSF levels of Aß42, an established biomarker for AD. Upcoming studies have to evaluate advantages and disadvantages of both diagnostic methods in a clinical setting.

43 PROTECTIVE EFFECTS OF MINOCYCLINE ON WHITE MATTER DEVELOPMENT AFTER NEONATAL HYPEROXIA

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Impaired neurological outcome in preterm infants is often associated with white matter damage and hypomyelination. Causes can be perinatal inflammation or hyperoxia. Minocycline has been demonstrated in animal models to protect the immature brain against inflammation and hypoxia-ischemia by microglial inhibition. In this study, we investigated benefits of minocycline on oligodendroglia and microglia of the immature white matter exposed to hyperoxia.We used a hyperoxia model in neonatal rats providing 24h exposure to 80 % oxygen concentration from P6 to P7. We analyzed whether minocycline blocks activation of microglia and attenuates or prevents damage of oligodendroglial precursor cell development, and whether acute treatment of hyperoxia-exposed rats with minocycline improves long term white matter integrity. Administration of minocycline during hyperoxia reduced apoptotic cell death and in improved both proliferation and maturation of oligodendroglial precursor cells (OPC). The use of minocycline blocked changes in microglial morphology and IL-1β release in rats exposed to hyperoxia. In microglial cultures, minocycline inhibited cytokine release while in mono-cultures of OPCs, it improved survival and proliferation. Long term impairment of white matter diffusivity in MRI with diffusion tensor imaging in P30 and P60 animals after neonatal hyperoxia was significantly attenuated by minocycline. Minocycline protects white matter development against oxygen toxicity through direct protection of oligodendroglia and by microglial inhibition. Moreover, long term benefits of postnatal minocycline treatment were seen in improved white matter integrity at young adult ages.

44 QUANTITATIVE ASSESSMENT OF BLOOD-BRAIN BARRIER PERMEABILITY AND CELL DAMAGE AFTER CORTICAL ISCHEMIA - ROLE OF FREE RADICALS

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Stroke is one of the leading causes of death and morbidity worldwide and its treatment remains a clinically unmet challenge. The ischemic brain is typically characterized by an ischemic core and a peri-ischemic zone prone to undergo cell damage. The peri-ischemic brain may either recover or deteriorate, leading to secondary stroke progression involving complications, e.g. increasing intracranial pressure, hemorrhagic transformation, delayed cognitive decline and epileptogenesis. Recently, blood-brain barrier (BBB) dysfunction has been indicated as a potential common denominator for post-stroke complications. However, to date methods to quantify BBB permeability and cell damage in-vivo are limited. Here we introduce a novel imaging technique designed to investigate the spatial and temporal correlation of BBB dysfunction and cell damage in-vivo in the peri-ischemic region of rose bengal-induced neocortical photothrombosis. BBB permeability and cell damage were assessed in rats through pial surface imaging (open cranial window method) following the peripheral injection of the tracer molecules fluorescein sodium salt (BBB permeability) and propidium iodide (PI, cell damage). We demonstrate that BBB permeability increases most prominently in the perfused region surrounding the ischemic core within minutes after thrombus formation. The region of augmented vascular permeability gradually expands and is associated with increasing uptake of PI into cells, suggesting progressive cellular damage within the peri-ischemic brain. In addition, we give preliminary evidence that inhibition of free radical signaling reduced the progression of cell damage, however did not affect BBB permeability in the peri-ischemic brain. This implicates that BBB dysfunction is not driven by parenchymal cell damage and may rather be due to blood-born signaling pathways. The debate whether BBB dysfunction increases cell damage remains open and demands future studies.

45 DETECTION OF DISTINCT HUMAN HUNTINGTIN PROTEIN SPECIES USING ANTIBODY-BASED ASSAYS

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Huntington`s disease (HD) is a neurodegenerative disorder caused by an abnormal extension of a polyglutamine (polyQ) tract (>35Q) that is located at the N-terminus in the protein huntingtin (HTT) [1]. Monomeric HTT with an expanded polyQ tract forms different types of aggregate species, including oligomers, protofibrils and eventually large amyloid-like fibrils in patient neurons [2]. Since the toxicity of specific HTT aggregate species remains unclear, it is necessary to develop novel tools in order to detect and quantify specific HTT protein assemblies. The use of antibodies is a promising approach to monitor HTT aggregation due to their high specificity and applicability in fluorescence-based detection methods such as, for example, time-resolved-Förster resonance energy transfer (TR-FRET) assays.
Here, we examined the aggregation of two recombinant HTT protein fragments in cell-free assays. We systematically investigated the protein Exon1Q49, a short N-terminal HTT fragment with 49 glutamines (~90 amino acids) as well as the protein Heat2Q73, a 900 amino acid long HTT fragment with 73 glutamines. To analyze the aggregation of the two HTT fragments, we utilized a panel of commercial and in-house antibodies. Native dot blot and filter trap assays revealed the formation of various types of insoluble HTT aggregate species. Moreover, we observed the formation of HTT aggregate species in a newly established TR-FRET immunoassay. Overall, we identified specific antibody combinations that can be used in the future to distinguish between small monomeric protein species and large insoluble aggregates. These tools may be suitable to study and quantify HTT protein aggregation in neurons of HD patients.

46 COGNITIVE FUNCTION IN PATIENTS WITH ADDISON'S DISEASE

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Addison's disease (AD) is characterized by lack of cortisol and aldosterone production. Therefore, patients need to replace these hormones predominantly using hydrocortisone and fludrocortisone that act via glucocorticoid (GR) and mineralocorticoid receptors (MR). GR and MR are closely related to cognitive function. However, very little is known about cognitive functioning and its potential association with GR or MR occupation in patients with AD. First, it is examined by a between-subject design whether patients with AD show worse cognitive functioning compared to healthy controls. Second, a repeated measures within-subject design is used to determine whether cognitive functions in patients with AD depend on MR function. 30 patients with AD are tested and compared to 30 age-, sex- and education-matched healthy controls. Each participant is examined twice with one week apart. Patients with AD are tested on one occasion after fludrocortisone intake (high MR occupation) and on the other occasion prior to fludrocortisone intake (low MR occupation). All patients with AD keep their stable regimen of hydrocortisone. Assessment includes executive function, concentration, and verbal, visual, working, as well as autobiographical memory. We hypothesize that AD patients exhibit worse cognitive function than healthy controls and assume that cognitive function in patients with AD depends on MR occupancy. Therefore, we expect that cognitive function will be better during high compared to low MR occupation. Results will be presented. Our study will improve the knowledge on cognitive function relative to MR occupation. Thus, the results might improve treatment options and quality of life in patients with AD and may additionally highlight the role of the MR on cognition in general.

47 INTERACTION OF THE COHEN SYNDROME-ASSOCIATED PROTEIN COH1 WITH RAB6 EMPHASIZES ITS ROLE FOR GOLGI FUNCTION AND NEURITOGENESIS

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Postnatal microcephaly, non-progressive mental retardation, and progressive retinal dystrophy are major features of autosomal recessive Cohen syndrome, which is caused by loss-of-function mutations in COH1 (VPS13B). Although a partial homology to Vps13p has been found, the biochemical characteristics, cellular localization, or functional role of the COH1 protein (3997aa) remained undefined.

Recently, our cell biological characterization identified COH1 as Golgi-enriched scaffold protein important for maintaining the Golgi network integrity. To identify molecular interactions of COH1, we screened the Vps13p interaction network for proteins involved in Golgi maintenance and membrane trafficking. Investigating Golgi-associated candidates, we found strong co-localization of COH1 with RAB6 in mammalian cells. Moreover, COH1 preferentially co-immunoprecipitated with the constitutive active RAB6 Q72L mutant. Consistent, inactivation of RAB6 by RNAi-mediated depletion or by overexpression of constitutive inactive RAB6 T27N mutant showed decreased membrane recruitment of COH1. Together our results point to a role of COH1 as a downstream effector protein of RAB6. Experiments in primary rat neurons showed that depletion of Coh1 negatively interfered with neurite extension. This provides a causal link between RAB6-dependent integration of Golgi-derived membrane traffic and membrane expansion during axonal growth. Our collective data suggest that neurological symptoms in Cohen syndrome may be due to deficient COH1 function in Golgi-derived membrane traffic during neuronal differentiation.

48 INTERPLAY OF AUTOPHAGY AND HEXOKINASE II AND THEIR ROLE IN NEURONAL CELL PROTECTION

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Extensive regulation of autophagy, glycolysis and oxidative phosphorylation (OXPHOS) contribute to the balance between biogenesis and degradation. Disruption of this balance leads to a broad spectrum of diseases including neurodegeneration. Despite controversial debates 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 (Pea-15) mediate cytoprotection after hypoxia but promote apoptosis in response to glucose deprivation. Cell death and autophagy are partly regulated by the same mechanisms. Thus, we here investigate the interplay between HKII / Pea-15 and different regulatory mechanisms of cell metabolism. To study autophagic activity we performed western blotting and immunofluorescence staining of the microtubule-associated protein 1 light chain 3 (LC3) and analysed Sequestosome 1 (SQSTM1, p62) expression under different deprivation conditions in cortical neurons of wild type and Pea15 knock-out mice and wild type rats. We showed an increased LC3-II / LC3-I ratio and a decreased p62 expression in neurons under starvation independent of Pea-15. Measurements with the XFe Extracellular Flux Analyzer also revealed a B27 dependent and Pea-15 independent regulation of glycolysis and oxidative respiration. To assess the impact of autophagy in ischemia we will use the OGD model (oxygen-glucose deprivation) in combination with autophagy inhibitors and inducers, respectively. In addition, HKII overexpression and knock-down will clarify the role of HKII in neuronal autophagy. The results clearly indicate autophagy regulation in neurons under deprivation conditions. Contribution of autophagy to neuronal survival under ischemic conditions has to be investigated.

49 HYPOTHALAMIC THYROID HORMONE SENSING REGULATES TORPOR INDUCTION

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A variety of hormones and neuroendocrine factors have been implicated in the induction of torpor, a reversible lowering of energy expenditure and body temperature during times of scarce food. Thyroid hormones (TH) belong to this regulatory network of torpor induction. Access of TH to the hypothalamus depends on transmembrane transporters like monocarboxylate transporter 8 (Mct8). Mct8 is the most specific TH transmembrane transporter and is expressed in hypothalamus, pituitary and other organs. We have taken advantage of our Mct8-deficient mouse model to study torpor. Based on hypothalamic deiodinase gene expression, male and female Mct8-deficient mice represent two different models distinguished by hypothalamic hypo- vs. hyperthyroidism. Accordingly, Tshβ expression is high in Mct8-/y and low in Mct8-/- pituitary possibly associated with diverging circulating T4 levels. Interestingly, 24 hours of fasting invariably induces torpor only in the hypothalamic hyperthyroid situation.

TH elimination is greatly enhanced during torpor probably mediated by augmented hormone sulfation and deiodination in the liver. Induction of torpor in female Mct8-deficient mice occurs independent of previously identified changes in leptin and Fgf21. These findings underscore the basal role of TH handling and sensing for the regulation of energy metabolism not only in peripheral tissues, but also in the hypothalamus.

50 AUTOSOMAL RECESSIVE PRIMARY MICROCEPHALY, MORE THAN JUST A NEURAL PROGENITOR PROLIFERATION DEFECT?

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Anatomy, Cell Biology and Neurobiology

Autosomal recessive primary microcephaly (MCPH) is characterized by severe microcephaly at birth and intellectual deficit. Microcephaly is secondary to a reduction of brain volume, which concerns particularly the cerebral cortex, and is acknowledged as a predominant grey matter disease. MCPH3 is caused by biallelic mutations in Cycline-dependent kinase 5 regulatory subunit-associated protein 2 gene CDK5RAP2. Cdk5rap2 mutant or Hertwig's anemia mice, which arose from a heavily irradiated mouse, have small brains and thin cortices already at early stages of neurogenesis during embryonal development. These mice were originally known for their hematopoietic phenotype and only the recent identification of an exon 4 inversion in the Cdk5rap2 gene led to their neurological assessment and their identification as a MCPH model. Cdk5rap2 is a centrosomal protein highly expressed in the neural progenitor pool. Its loss results in increased cell-cycle exit of progenitors and subsequent premature neuronal differentiation and depletion of the progenitor pool. Still, further mechanisms have been proposed to exist, and the exact effect of a loss of Cdk5rap2 function on neurogenesis and neuronal differentiation is not known. Here, we report the effects of loss of Cdk5rap2 function on neurogenesis and on the differentiation of neocortical neurons in Hertwig's anemia mice. In addition to the significant gross reduction of the brain size with predominant reduction of the upper cortical layer in these mice, we demonstrate findings in line with a midline defect with abnormal corpus callosum morphology. In order to detect possible changes in morphology/arborization of neocortical neurons, we are currently applying Golgi staining and GFP in utero electroporation. Homozygous mutant mice further exhibit eye abnormalities, have reduced testis sizes, lack uterus and ovaries, and female mice are infertile. Our findings indicate that Cdk5rap2 possesses further functions than the regulation of neural progenitor proliferation.

51 SYNAPTIC PLASTICITY INDUCED BY GAMMA FREQUENCY OSCILLATIONS

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The hippocampal network shows three main types of in vivo oscillatory activity pattern in a behavioral-dependent manner: theta, gamma and sharp wave-associated field ripple oscillations. Oscillations in the gamma frequency band are receiving particular attention for their possible role in memory formation and neuronal plasticity, but it is still unknown whether this rhythm represents a network state that promotes the formation of long-lasting synaptic plasticity within the hippocampal network. We analyzed the synaptic and firing properties of the hippocampal CA3 pyramidal cells in the active network. Extracellular recordings were obtained from the stratum pyramidale of the CA3 area. Our data show that pharmacologically induced gamma frequency oscillations lead to activity-dependent modification in the hippocampal CA3 network in vitro. Gamma rhythms influence subsequent network activities including sharp wave-ripple complexes, and lead to synaptic plasticity in hippocampal principal neurons. Network oscillation induced synaptic plasticity, expressed as long-lasting increases in sharp wave-ripple-associated synaptic currents, exhibits reinforced excitatory synaptic strength at pyramidal cell-pyramidal cell synapses. We conclude that gamma oscillations represent a network state that lead to long-lasting synaptic plasticity and may enhance the reliability of signal transmission in the CA3 network.

Bernstein Center for Computational Neuroscience

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 strongly research oriented and accepts up to 15 students per year. Language of instruction is English. The structured PhD Program is financially supported by the Training Research Group 1589/2 "Sensory Computation in Neural Systems" funded by the Deutsche Forschungsgemeinschaft (DFG).

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Center for Stroke Research Berlin (CSB)

BMBF-Fördernummer 01 EO 1301

Our goal is to expand the limited field of possibilities in stroke therapy through a dialogue between patient-oriented research and basic research and thus improve the quality of life for those afflicted by this severe disease. Stroke itself is a sudden event, but over half its victims are left in its wake with chronic neurological and neuropsychological deficits. This makes stroke the most common cause in Germany of permanent disabilities acquired in adulthood. For this reason we consider stroke a chronic disease; patients must be supported with research and therapy from the moment the disease strikes, in its acute treatment through to rehabilitation and beyond. This was the impetus for creating the Berlin Stroke Alliance, an alliance of organizations and care providers spanning the gamut from acute hospitals and rehabilitation clinics through to providers of assisted living facilities. Stroke has a complex pathophysiology, so its occurrence and the development of damage in the brain can only be researched and treated with a comprehensive overview of the processes active in the brain, heart and vascular system as well as in the immune system. The CSB was thus founded and built as an interdisciplinary center working with neurologists, neurosurgeons, immunologists, cardiologists, radiologists and epidemiologists.

Research Fields
Protect Brain: Brain protection is possible. The CSB aims to discover novel mechanisms and treatments, identify suitable patients, and explore new ways to facilitate treatment.

Prevent Complications: Post-stroke complications contribute substantially to stroke morbidity and mortality. The CSB will identify and target such complications and provide a novel comprehensive concept of stroke management.

Restore Function: Many patients receive a rehabilitation therapy after stroke. Few of the approaches are evidence-based. The CSB aims to provide new evidence by means of novel registers and rehabilitation trials.

Spokesperson
Prof. Dr. Ulrich Dirnagl

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CSB
Center for Stroke Research Berlin

International graduate program Medical Neurosciences From basic science to translational research

The MSc program Medical Neurosciences is hosted at the Charité and offers a research focused training for natural scientists and medical doctors alike. It aims to deliver a thorough academic education which qualifies for a further career in the basic neurosciences as well as in translational, bench-to bedside research. The MSc program is divided into 9 modules including smaller research projects (laboratory rotations) and the concluding Master thesis.
The program structure enables MSc students to develop an individual curriculum that can be tailored to their interest and specific research and training needs. Accompanying lectures and complementary skill courses ensure an ideal training for a further career in translational neuroscience.
The 3-year PhD program consists of a personalized curriculum, which supplements and supports the main research project. The individual backgrounds as well as the requirements of the thesis project are taken into account when constructing this individual curriculum. At this stage, special care is taken to train and sensitize students for important non-academic skills like financial accounting, legal issues, grant proposal writing, and communication to prepare them for the next career step. Furthermore, opportunities to foster early independence are continuously offered. The PhD degree is awarded based on at least three publications or a dissertation.

Spokesperson: Prof. Dr. Helmut Kettenmann

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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. In 2012, the School started a structured English-language postdoctoral program offering networking activities, workshops, teaching portfolio, supervision training, and other career development opportunities for researchers. As a result of the highly successful funding bid within the second national Excellence Initiative competition, in October 2013 the new research-based, English-language master's program "Mind and Brain" (M.Sc./M.A.) has started.

The focus of research at the School is on the interface between the humanities and behavioral sciences with the neurosciences. Main topics of research are: 'conscious and unconscious perception', 'decision-making', 'language', 'brain plasticity and lifespan ontogeny', 'mental disorders and brain dysfunction', and 'human sociality and the brain'. The School has a faculty comprised of 60 distinguished researchers, including five Max Planck directors, four Leibniz Prize winners, several ERC advanced grant recipients, and the Einstein Visiting Fellow. Together with the associated research groups they cover the most relevant research areas in the mind and the brain sciences.

Hosted by the Humboldt-Universität zu Berlin, the School's research program includes scientists from Freie Universität, Charité, Technical University, Bernstein Center for Computational Neuroscience Berlin, Max Planck Institute for Human Development, and Max Planck Institute for Human Cognitive and Brain Sciences in Leipzig and the universities of Leipzig, Potsdam, and Magdeburg.

Currently the School has 45 doctoral student members, 34 alumni, 57 faculty members, 12 postdocs and 25 master's students. There is also a continuously growing number of associated researchers and associated research groups.

The School closely collaborates with six neuroscience graduate schools in Berlin (Neuroscience Berlin). It is a member of Neuroschools Germany and of the Network of European Neuroscience Schools (NENS).

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

NeuroCure – Towards a better outcome of neurological disorders is a cluster of excellence in the neurosciences at the Charité - Universitätsmedizin Berlin funded through the Excellence Initiative of the German federal and state governments. With financing until the year 2017, the internationally visible, interdisciplinary consortium focuses on researching neurological and psychiatric disease mechanisms and the transfer – or translation – of knowledge from basic science to clinical practice.

NeuroCure's substantial funding is applied by the partner institutions Humboldt-Universität zu Berlin, Freie Universität Berlin, and non-university research institutions Max Delbrück Center for Molecular Medicine (MDC), Leibniz Institut für Molekulare Pharmakologie (FMP) and German Rheumatism Research Centre Berlin (DRFZ) to expand the well-established neuroscience community in Berlin by strengthening the network of current research activities and establishing more than 20 new professorships and junior research groups.

With the goal of transferring insights gained from basic science to clinical studies and developing new therapies and diagnostic approaches, NeuroCure is active primarily in the areas of cerebrovascular diseases, neuroinflammation, neurodegeneration and disturbances of functional network structures, with particular emphasis on diseases such as stroke, multiple sclerosis, Alzheimer's disease, epilepsy and developmental disturbances. The focus is not only on the underlying disease mechanisms common to these afflictions but also on the overarching research approaches and concepts. NeuroCure addresses these topics in seven thematic research areas: mechanisms of damage, endogenous neuroprotection, regeneration, crosstalk between nervous and immune system, developmental disturbances, molecular neuropathologies of ion channels and transporters, and plasticity. In addition, the cluster is expanding various clinical and technological infrastructures with central know-how that can be shared by all scientists.

Spokesperson: Prof. Christian Rosenmund

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NEUROCURE
Cluster of Excellence

BMBF-VIP0272, AZ 03V0364
Opioid Analgesics Devoid of Side Effects through Computational Drug Design

In this project we investigate new analgesics developed by computer-assisted drug design. Currently available strong analgesics (opioids) are limited by major adverse effects such as sedation, respiratory depression, tolerance, addiction or constipation, resulting in extensive additional costs due to complications. We aim at novel opioids acting selectively at the site of injury to avoid such side effects. Following injury, opioid receptors on peripheral sensory neurons are upregulated, their G-protein coupling, signaling and recycling is enhanced, and their activation results in potent inhibition of neuronal excitability and analgesia. The augmented signaling suggests conformational changes of opioid receptors or ligands in the inflamed environment. In collaboration with the Zuse Institute for Applied Mathematics in Berlin, we simulate the conformations of opioid receptors and their agonists, synthesize new compounds and verify their effects in vitro and in vivo in models of pathological pain.

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BMBF consortium e:Bio 0316177B / C1
The Nociceptor Pain Model ("NoPain")

This project applies systems-medicine-based mathematical models of signaling switches involved in pain sensitization, optimizes and expands them by reflection on molecular, cellular as well as animal experiments, to finally translate this knowledge and test the predictive potential in humans. We hypothesize that opioids will modulate cAMP-dependent and other pathways identified by computational simulation. Ultimately we aim at testing novel analgesic compounds in human patients identified as most suitable, aiming at mechanism-based pain therapy.
The consortium comprises groups from across Germany, representing medical, bioinformatic and biochemical backgrounds, including Anesthesiology, Charité-Universitätsmedizin, CBF, Berlin; Anesthesiology, Uniklinik, Köln; Neurology, Universitätsklinikum Schleswig-Holstein, Kiel; Systems Biology, Otto von Guericke, Universität Magdeburg; Computer Science, Brandenburg University of Technology, Cottbus; and Biochemistry, University Kassel.

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EU consortium FP7-HEALTH-2013-INNOVATION-1 No. 602891-2 Neuropathic Pain: Biomarkers and Druggable Targets within the Endogenous Analgesia System ("NeuroPain")

The search for new analgesics has been difficult in part due to the poor predictive validity of currently available animal models of chronic pain. In this consortium we aim at overcoming these obstacles by an interdisciplinary collaboration between basic science groups, clinicians and leading private companies from Germany, Spain, UK, France, Poland, Finland and Iceland. We will validate new animal models to evaluate the electrophysiological, behavioral, emotional and cognitive manifestations of neuropathic pain and the effectiveness of novel compounds. The use of these models in combination with other behavioral paradigms and new conditional knockout mouse lines for components of the endogenous opioid and cannabinoid system will permit the identification of novel druggable targets and biomarkers for neuropathic pain. Novel analgesic compounds acting on these endogenous systems developed by private companies will be tested. Clinical studies should identify biomarkers for neuropathic pain using genetic approaches and will investigate treatments with a translational focus based on cross validation of the findings in animals and humans.

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BMBF Consortium
Neuroimmunology and Pain („Neuroimpa“)

The overall aim of this consortium is to explore the potential of neuro-immune interactions for novel therapeutic approaches in musculo-skeletal diseases. On the one hand, we examine neuronal processes contributing to the generation and maintenance of pathological changes. On the other hand, we aim at improving pain by influencing interactions between the nervous and immune systems that activate and sensitize the nociceptive system. Specifically, we try to elucidate the following questions: What is the therapeutic potential of blocking or promoting efferent somatosensory and autonomic neuronal functions in arthritis and osteoporosis? What is the analgesic potential of neutralizing mediators produced by immune cells? Is the inhibition of the pathological process correlated with the inhibition of pain? What is the therapeutic potential of activating peripheral opioid receptors by exogenous or endogenous agonists in the control of inflammation and pain? Is the success of such strategies dependent on certain (e.g. inflammatory vs. destructive) stages of the disease? Are these novel therapeutic strategies applicable to different diseases such as rheumatoid arthritis, osteoarthritis or osteoarthrosis?

Partners: Kamradt (Jena), Grässel (Regensburg), Schaible (Jena, coordinator), Schett (Erlangen), Chang (Berlin), Stein (Berlin), Sieper (Berlin).

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SFB Transregio 43
"The Brain as a Target of Inflammatory Processes"

The Sonderforschungsbereich/Transregio (SFB TRR) 43 was launched in 2008 as a transregional research venture between Berlin and Göttingen, in which the Charité - Universitätsmedizin Berlin and the University of Göttingen cooperate with the independent research institution Max Delbrück Center for Molecular Medicine (Berlin-Buch), Max Planck Institute for Experimental Medicine (Göttingen) and Max Planck Institute for Infection Biology (Berlin).
The scientific basis of the SFB TRR 43 is the recent insight that immunological processes are not only involved in classical inflammatory disorders of the central nervous system (CNS) such as multiple sclerosis, but also appear to play a major role in the pathogenesis of primarily non-inflammatory or rather "atypical" neuroimmunological pathologies, such as stroke – both ischemic and hemorrhagic –, brain tumors, and neurodegenerative disorders. In any of these conditions or disorders, immune cells interact with cells of the nervous system via complex signalling cascades. Besides a local crosstalk between cells of the nervous and the immune systems there is increasing evidence that CNS alterations in turn also impact systemic immune responses, which may facilitate either life-threatening (systemic) infections or protect CNS tissue by modulating local CNS actions. Although the initiating, pathogenetically relevant events may differ considerably between various CNS diseases, they seem to utilize common pathways in the (bidirectional) crosstalk between the immune and the nervous system. Deciphering these common pathways is an essential bond and common denominator of the SFB TRR 43 consortium in order to enable the design of regimens that modulate various CNS diseases irrespective of their specific pathogenesis or etiology.

Spokesperson: Prof. Dr. Frank Heppner (Berlin)

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SFB TRR 43 | The Brain as a Target of Inflammatory Processes

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