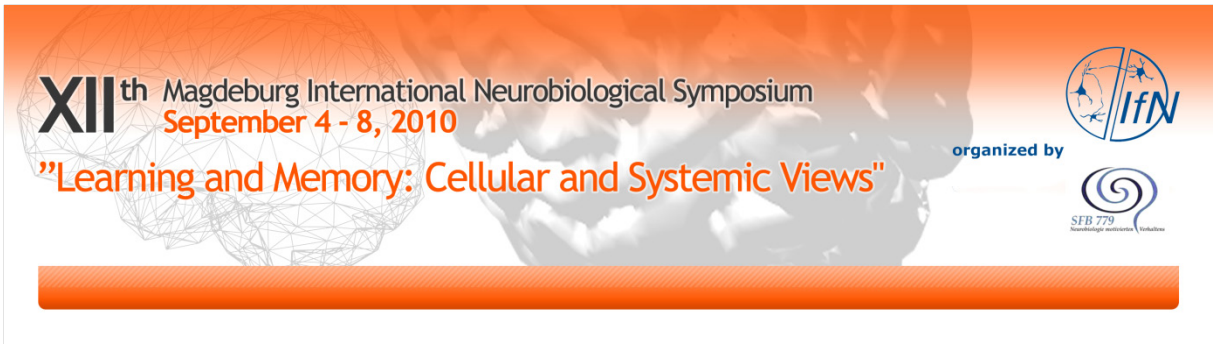

Program and Abstracts

cbbs
center for behavioral brain sciences

XIIth Magdeburg International Neurobiological Symposium
"Learning and Memory: Cellular and Systemic Views"

September 4 – 8, 2010

Herrenkrug Hotel Magdeburg

Program Committee:

- Julietta U. Frey
- Emrah Düzel
- Eckart D. Gundelfinger
- Volker Höllt
- Volkmar Leßmann
- Thomas Münte
- Frank Ohl
- Henning Scheich
- Ariel Schoenfeld
- Constanze Seidenbecher
- Oliver Stork

6 Sessions:

- Reward & Punishment in Learning
- Neurodegeneration and Learning
- Molecular Memory Concepts
- Physiology and Pathology of Learning
- Late Associativity
- Spike-Timing- and Oscillation-Dependent Plasticity

Evening Lecture:

- Hans-Jürgen Matthies Honorary Lecture by Ivan Izquierdo, Porto Alegre

Sponsors

We wish to thank all our sponsors for their collaboration and financial support:

- Deutsche Forschungsgemeinschaft
- Leibniz Institute for Neurobiology (IfN)
- SFB 779 “Neurobiology of Motivated Behavior”
- Center for Behavioral Brain Sciences (CBBS)
- Novartis Deutschland GmbH
- Janssen-Cilag GmbH
- Eisai Deutschland

Private donations to support the continuation of scientific lifetime achievements of Prof. Hans-Jürgen Matthies:

Prof. Klaus Reymann

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Prof. Eckart Gundelfinger

Dr. Thomas und Dr. Constanze Seidenbecher

Jürgen Clausen

The German Collaborative Research Center "Neurobiology of Motivated Behavior"

The German Collaborative Research Center (Sonderforschungsbereich) SFB 779, funded by the Deutsche Forschungsgemeinschaft (DFG) since 2008, is a consortium of scientists from various disciplines and institutions in Magdeburg investigating the neuronal basis of animal and human behavior.

Specifically, this consortium focuses on the question of how behaviors are motivated, in particular as a consequence of received feedback to previous behaviors from the environment. The consortium considers central to this endeavor the investigation of

- the neuronal mechanisms of feedback-evaluation
- the interaction of feedback-evaluating brain systems with functions like perception, attention, learning and memory
- the underlying cell-physiological and molecular processes, as well as
- the pathophysiology of motivation during disease.

To this set of aims, the SFB 779 has brought together scientists from the Science Faculty (Institutes of Biology, Psychology and Experimental Physics) and the Medical Faculty (Clinic for Neurology, Clinic for Psychiatry, Institutes of Pharmacology, Anatomy, Physiology and Experimental Inner Medicine), as well as from the Leibniz Institute for Neurobiology (IfN) and associated institutions. The SFB 779 has developed experimental paradigms allowing researchers from various disciplines (behavioral neuroscience, systems neurophysiology, molecular biology, clinical neuroscience) to collaborate on the same experiment, thereby facilitating very close interaction between these disciplines.

The SFB 779 is delighted to co-organize the XIIth Magdeburg International Neurobiological Symposium and welcomes all international guests to Magdeburg.

Prof. Frank Ohl
Coordinator of the SFB 779

Program

	Morning Session 9 p.m. – 12:30	Afternoon Session 2.30 p.m. – 6 p.m.	Evening
Saturday, 04.09.10	----	Registration, Hanging of Posters 6 p.m. – 9 p.m.	Welcome Reception 7 p.m.
Sunday, 05.09.10	**1. Reward & Punishment in Learning** 1.1 Shihab A Shamma 1.2 Randy Gallistel 1.3 Angela Kolodziej - Coffee Break - 1.4 Hagai Bergman 1.5 Christian Büchel	**2. Neurodegeneration and Learning** 2.1 Andreas Papassotiropoulos 2.2 Thomas Münte 2.3 Emrah Düzel - Coffee Break - 2.4 André Fischer 2.5 Lennart Mucke	**Hans-Jürgen Matthies Honorary Lecture** Ivan Izquierdo - Barbecue
Monday, 06.09.10	**3. Molecular Memory Concepts** 3.1 Erin Schuman 3.2 Bong-Kiun Kaang 3.3 Ronald L. Davis - Coffee Break - 3.4 EunJoon Kim 3.5 Kobi Rosenblum	**4. Physiology and Pathology of Learning** 4.1 Ingrid Ehrlich 4.2 Amy Milton 4.3 Rainer Spanagel - Coffee Break - 4.4 Kerstin Krauel 4.5 Andreas Heinz	**Meeting Dinner**
Tuesday, 07.09.10	**5. Late Associativity** 5.1 Wayne Sossin 5.2 Daisuke Okada 5.3 Arvind Govindarjan - Coffee Break - 5.4 Maria C. Martinez 5.5 Dorothee Heipertz	**6. Spike-Timing and Oscillation dependent Plasticity** 6.1 Nelson Spruston 6.2 Elke Edelmann 6.3 Andreas Draguhn - Coffee Break - 6.4 Dietmar Schmitz 6.5 Thomas Klausberger Poster Removal	**Speakers´ Dinner at the Farm**
Wednesday, 08.09.10	Departure	----	----

Sunday, September 05

Morning Session 9 a.m.
Introductory Remarks
Frank Ohl, Coordinator of the Collaborative Research Center "Neurobiology of motivated behavior"

1. Reward & Punishment in Learning
Chairs: Thomas Münte & Frank Ohl

9.10 – 9.40 **Shihab A Shamma, Maryland**
„Adaptive neural processing during aversive and appetitive behaviors"
9.45 – 10.15 **Randy Gallistel, Rutgers, NJ**
„Memory and the computational brain"
10.20 – 10.50 **Angela Kolodziej, Magdeburg**
„Auditory Learning in rodents with appetitive and aversive reinforcers"

10.55 – 11.25 Coffee Break

11.25 – 11.55 **Hagai Bergman, Jerusalem**
„Information processing in the critic-actor networks of the basal ganglia"
12.00 – 12.30 **Christian Büchel, Hamburg**
„Prediction Errors in Human Learning"

12.35 – 14.30 Lunch

Afternoon Session 2.30 p.m.

2. Neurodegeneration and Learning
Chairs: Björn Schott & Ariel Schoenfeld

14.30 – 15.00 **Andreas Papassotiropoulos, Basel**
„Genetics of human memory: From physiology to disease"
15.05 – 15.35 **Thomas Münte, Lübeck**
„Neuroimaging approaches to study functional and structural changes in neurodegeneration"
15.40 – 16.10 **Emrah Düzel, Magdeburg**
„Functional Phenotyping of Successful Aging in Long-Term Memory"

16.15 – 16.45 Coffee Break

16.45 – 17.15 **André Fischer, Göttingen**
„The epigenome of neuropsychiatric diseases"
17.20 – 17.50 **Lennart Mucke, San Francisco**
„Mechanisms Underlying Cognitive Deficits in Models of Alzheimer´s Disease"

Hans-Jürgen Matthies Honorary Lecture
Chair: Klaus Reymann

18. 30 – 19.30 **Ivan Izquierdo, Porto Alegre**
"Memory persistence"

19.30 Barbecue at Herrenkrug Terrace

Monday, September 06

Morning Session 9 a.m.

3. Molecular Memory Concepts
Chairs: Eckart Gundelfinger & Constanze Seidenbecher

9.00 – 9.30 **Erin Schuman, Frankfurt**
„Local Control at Synapses“
9.35 – 10.05 **Bong-Kiun Kaang, Seoul**
„Role of PI3K in synaptic plasticity and memory“
10.10 – 10.40 **Ronald L. Davis, Houston**
„Memory traces of Drosophila olfactory learning“

10.45 – 11.15 Coffee Break

11.15 – 11.45 **EunJoon Kim, Daejeon**
„Roles of Rac 1-regulatory proteins in synaptic plasticity and learning and memory“
11.50 – 12.20 **Kobi Rosenblum, Haifa**
„Protein A vailability in the Cortex and Memory Consolidation: The Taste Case“

12.30 – 14.30 Lunch

Afternoon Session 2.30 p.m.

4. Physiology and Pathology of Learning
Chairs: Volker Höllt & Henning Scheich

14.30 – 15.15 **Ingrid Ehrlich, Tübingen**
„Learning induced plasticity in the amygdala“
15.20 – 15.50 **Amy Milton, Cambridge**
„CS-drug memory reconsolidation and the prevention of relapse“
15.55 – 16.25 **Rainer Spanagel, Mannheim**
“Alcoholism: A Systems Approach from Genes to Addictive Behaviour”

Poster Session

16.30 – 17.30 Coffee and Posters

17.30 – 18.00 **Kerstin Krauel, Magdeburg**
“Reward dependent learning in children and adolescents with attention deficit hyperactivity“
18.05 – 18.35 **Andreas Heinz, Berlin**
“Neurobiology of reward systems: relevance for learning, addiction and psychosis”

20.00 Meeting Dinner at Herrenkrug Ballroom

Dinner Speech
Henning Scheich

Tuesday, September 07

Morning Session 9 a.m.

5. Late Associativity
Chairs: Julietta Frey & Emrah Düzel

9.00 – 9.30 **Wayne Sossin, Montreal**
„Translational control during memory; how the translational apparatus is tuned to produce distinct proteins from different inputs“

9.35 – 10.05 **Daisuke Okada, Tokyo**
„Input-specific spine entry of soma-derived Vesl-1S protein conforms to synaptic tagging“

10.10 – 10.40 **Arvind Govindarjan, Boston**
„The dendritic branch is a unit of storage for long-term memory engrams“

10.45 – 11.15 Coffee Break

11.15 – 11.45 **Maria C. Martinez, Buenos Aires**
„Bringing synaptic tagging into behavior“

11.50 – 12.20 **Dorothee Heipertz, Magdeburg**
„Behavioral tagging in humans: Enhancement of memory in the context of novelty“

12.30 – 14.30 Lunch

Afternoon Session 2.30 p.m.

6. Spike-Timing and Oscillation dependent Plasticity
Chairs: Volkmar Leßmann & Oliver Stork

14.30 – 15.00 **Nelson Spruston, Evanston**
„The role of backpropagating action potentials and dendritic spikes in the induction of LTP at synapses on hippocampal CA1 pyramidal neurons“

15.05 – 15.35 **Elke Edelmann, Magdeburg**
„Stimulation paradigms inducing STDP in CA1: potential roles for dopamine and BDNF“

15.40 – 16.10 **Andreas Draguhn, Heidelberg**
„Definition of hippocampal cell assemblies“

16.15 – 16.45 Coffee Break

16.45 – 17.15 **Dietmar Schmitz, Berlin**
„Role of PRG-1 in synaptic transmission and epilepsy“

17.20 – 17.50 **Thomas Klausberger, London**
„Theta oscillations in the medial prefrontal cortex“

Concluding Remarks
Eckart Gundelfinger

19.30 Speakers' Dinner at the Farm

Lectures

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Abstracts of Poster Presentations

P01: Disruption of fear memory consolidation and reconsolidation by actin filament arrest in the basolateral amygdala
Bergado-Acosta JR 1, Rehberg K 1, Koch J 1, Stork O 1,2

P02: The effect of swim stress on hippocampal CA1-LTP and its modulation by the ventral tegmental area in freely moving rats
Yeritsyan NB1, Frey JU1

P03: Transgenic expression of the serine/threonine kinase Ndr2 increases hippocampal mossy fibre density and enhances open field exploration in mice
Rehberg K 1, Acosta-Bergardo JR 1, Schwegler H 2, Müller B 1, 3, Stork O 1,3

P04: NCAM knock out mice: a model for autistic features?
Albrecht A,1, Wolfer DP,2, Welzl H,2, Lipp HP,2, Stork O,1

P05: Early neuronal dysfunction by amyloid β oligomers depends on activation of NR2B-containing NMDA receptors
Rönicke R 1,7; Mikhaylova M 2; Rönicke S 3; Meinhardt J 4; Schröder UH 1; Fändrich M 5,6; Reiser G 3; Kreutz MR 2,7; Reymann KG 1,7

P06: Towards a network of synaptic protein interactions as a basis for dynamic modeling of synaptic signaling pathways
Pielot R 1, Oschmann J 1, Eisenschmidt E 2 Haus UU 2, Dieterich D 3, Smalla KH 1, Weismantel R 2, Gundelfinger E1

P07: Histone Modifications in Frontal Cortex of Neonatal Maternally Separated Mice
Xie L., Bock J.

P08: Superior memorizers recruit a small left lateralized network of brain areas when using the method of loci for encoding
Brechmann A1, Mallow J2, Scheich H3

P09: Are direct primary sensory cortex connections also made for learning and memory?
Budinger E, Scheich H

P10: The impact of sex, diurnal phase and conditioned stimulus modality on infant and adult two-way active avoidance learning in rats
C. Rockahr, M. Gruss, K. Braun

P11: Ontogeny of two-way active avoidance behavior: learning capacity in infant and adolescent rats may be determined by differential metabolic recruitment of prefrontal and limbic regions
Riedel A, Gruss M, Korz V, Bock J, Braun K

P12: Influence of electrical stimulation of the ventral tegmental area on field potentials in hippocampal CA1 of freely moving rats
Thomas Scherf, Julietta U. Frey und Sabine Frey

P13: Infant avoidance training blocks adult avoidance learning in mice
Maas A[1], Pinkernelle J[2], Braun K[1]

P14: Spatial and temporal dynamics of newly synthesized proteins in developing neural cells
Landgraf P 1, Antileo ER 1, Müller A 1, Kähne T 3, Richter K 4, Smalla KH 2, Dieterich DC[1]

P15: Frequency-dependent modulation of Spike Timing-Dependent Plasticity by brain-derived neurotrophic factor
Edelmann E, Lessmann V

P16: Impaired long-term plasticity at thalamic input synapses to projection neurons of the lateral amygdala in heterozygous BDNF knockout mice
Susanne Meis, Volkmar Lessmann

P17: How outcome expectations organize learned behaviour in larval Drosophila
Schleyer M 1,3, Saumweber T 1, Nahrendorf W[1], Fischer B[1], von Alpen D[2], Pauls D[2], Thum A[2], Gerber B[1]

P18: Bassoon and Piccolo interact with RIM-binding proteins and thereby regulate the localization of presynaptic calcium channels
Davydova D, Marini C, Bischof F, Romorini S, Altrock WD, Fejtova A, Gundelfinger ED

P19: Early stress experiences prevent emotional reinforcement of hippocampal long-term potentiation in adult male rats: active extinction of traumatic memories as a disease-protective
mechanism?
Wang H 1,2, Meyer K 1,2, Korz V 2,3

P20: Cell-selective visualization of newly synthesized proteomes in mammalian primary co-cultures and in Drosophila melanogaster
Müller A 1*, Kobler O 2*, Erdmann I 1, Landgraf P 1, Thomas U 2, Dieterich DC[1]

P21: Mapping Fucosylated Synaptic Proteins with Aleuria Aurantia Lectin and Click Chemistry
Höche N 1,2, Kähne T 4, Kobler O 3, Richter K 5, Tischmeyer W 1, Smalla KH[1], Dieterich DC[2]

P22: Electrical perforant pathway stimulation triggers enhanced BOLD responses in various target regions of the hippocampus subsequent the same stimulus was used as a conditioned stimulus for an active avoidance learning
Angenstein F 1,2, Krautwald K 3, Wetzel W[1], Scheich H[1]

P23: Activity-dependent remodelling of the presynaptic cytomatrix at the active zone
Lazarevic V[1], Schoene C 1,2, Heine M[2], Gundelfinger ED[1], Fejtova A[1]

P24: Auditory gating in the striatum and auditory cortex: Dynamics of cortical and striatal interactions and the effects of discrimination learning
Woldeit ML 1,2, Schulz AL[1] Ohl FW 1,2

P25: Phytoestrogen modulation of Glutamic Acid Decarboxylase (GAD) Expression and Conditioned Fear Behavior
Kiran Sandhu, Anne Albrecht, Jorge R. Bergado-Acosta, Bettina Müller and Oliver Stork

P26: Learning Driven by Reward and Punishment and the Neuromodulation of Acquisition, Retrival and Extinction of two way active avoidance learning by Brain Stimulation and Lesion
Anton Ilango[1], Jason Shumake[1,3], Angela Kolodziej[1], Imelda Pasley[1], Wolfram Wetzel[1], Henning Scheich[1], Frank W Ohl [1,2]

P27: Dopamine-modulated spike-timing-dependent-plasticity result in different learning rates for appetitive and aversive reinforcement
Rach S[1], Herzog A[1], Herrmann CS[1]

P28: Age-dependent impairment of fear learning in heterozygous BDNF knockout mice
Endres T, Lessmann V

P29: Surface mobility of neurexins at active synapses
Schneider R,[1], Niesmann K,[2], Missler M,[2], Heine M,[1]

P30: Molecular mechanisms of dopaminergic memory modulation
Reichenbach N[1], Kähne T[2], Schicknick H[1], Dieterich DC[1], Gundelfinger ED[1], Smalla KH[1], Tischmeyer W[1]

P31: Activity-dependent synaptic plasticity evokes Jacob translocation to the nucleus in hippocampal neurons after stimuli inducing long-term potentiation but not long-term depression
Mikhaylova M 1,4, Behnisch T 2,4, Parvez S 3,4, Bethge P[1], Yuan XPA[2] Frey JU[3], Kreutz MR[1]

P32: Dopaminergic Modulation of Learning-Dependent Plasticity in human auditory cortex?
Jörn M[1], Puschmann S[2], Thiel C[2], König R[1], Brechmann A[1]

P33: A dopamine agonist compensates for the LTP impairment resulting from amyloid ß oligomers
Janc OA 1, Rönicke R 2, Scheich H 2, Reymann KG 1,2

P34: Auditory working memory: Physiological mechanisms in human and monkey auditory cortex
Zacharias N[1], Huang Y[2], König R[1], Brosch M[2], Heil P[3]

P35: Role of different neuromodulators for the induction and maintenance of L-LTP in hippocampal basal CA1-dendrites
Ramachandran R, Fan W*, Parvez S and Frey JU

P36: A dynamic framework for cortical processing during learning
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P37: The effects of digestion of extracellular matrix on the network activity in neuronal cultures
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P38: Single-cell resolution mapping of neuronal activity in cerebral cortex using the K+-probe thallium as a tracer
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P39: shRNA mediated knockdown of proteins relevant for activity dependent secretion in neurons
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P40: Electrical properties of CA1 pyramidal neurons after RNA interference-mediated knockdown of BDNF in single CA1 pyramidal neurons
Daniel J[1], Brigadski T[1], Leßmann V[1]

P41: Haplodeficiency for GAD65 provides resilience in a mouse model of posttraumatic stress disorder
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P42: Neuronal activation in the primate auditory cortex during learning of bi-modal audio-visual task performance
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P43: Role of proteolysis in extracellular matrix remodeling
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P44: Jacob decodes in the nucleus the synaptic or extrasynaptic origin of NR2B-NMDA receptor signals
Anna Karpova1, Marina Mikhaylova1, Philipp Bethge1, Julia Bär1, Parameshwar Pasham Reddy1 , Rahul Rajkumar Kaushik1, Christina Spilker1, Werner Zuschratter2, Thilo Kähne4, Eckart D. Gundelfinger3, M

P45: Alteration of reward in an animal model of depression – the olfactory bulbectomy
Grecksch G[1], Becker A[1], Höllt V[1]

P46: Biological Basis for Individual Differences in Social Decision Making – Evidence in Genetics and fMRI
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P47: Oscillations in the human thalamus dissociate novel and familiar stimuli
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P48: Motivational salience specifically modulates repetition suppression in the anterior hippocampus
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P49: External Feedback Networks and Perceptual Learning
M. Grueschow1,2,3, H.-J. Heinze3, O. Speck4, J.-D. Haynes1,2

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P01: Disruption of fear memory consolidation and reconsolidation by actin filament arrest in the basolateral amygdala

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The importance of cytoskeletal reorganization for memory formation has been demonstrated in various studies, however, the temporal specifics of this process are still unresolved. Here, we investigated, in mice, the importance of actin filament dynamics in the basolateral complex of the amygdala (BLA) for the consolidation and reconsolidation of auditory cued fear memory. The fungal cytotoxin phalloidin was injected bilaterally into the BLA to arrest actin filaments at different time points (30 min, 6 h and 24 h) after fear conditioning training or fear memory retrieval. We found that phalloidin blocks consolidation and reconsolidation of auditory fear memory when injected 6 h after training or retrieval, respectively. No effects were observed on the animals' responses to the background context or neutral acoustic stimuli at this time. Also, no effect was observed when phalloidin was injected 24 h after training or memory re-activation, ruling out any interference with the retrieval or expression of conditioned fear. In contrast, injections performed 30 min after memory re-activation generally decreased defensive behavior upon reconsolidation. Together, these results indicate that dynamic re-arrangements of actin filaments occur in the BLA during specific phases of fear memory consolidation and reconsolidation, and support cellular processes involved in long-term information storage. Supported by grants from the German Research Foundation. KR was a scholar of the DFG graduate school 1167.

P02: The effect of swim stress on hippocampal CA1-LTP and its modulation by the ventral tegmental area in freely moving rats

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Stress exerts detrimental effects on memory such as through modifications of neuronal circuitry. Alterations in synaptic plasticity within the hippocampus can serve as one of such modifications. Depending on its severity and context, stress differentially influences hippocampal LTP, a cellular model used to study mechanisms of memory formation. The long-term maintenance of LTP requires spaced-associative, heterosynaptic interactions of glutamatergic and neuromodulatory inputs during its induction (Frey & Frey, 2008). Here, we approached swim-stress-induced associative changes of LTP in the hippocampal CA1 region. Given the powerful neuromodulatory impact of stress and the essential role that the hippocampal CA1 plays in the processing of spatial and temporal information, we studied the effect of mild swim stress presented at different time points before or after LTP-induction. Further, as the ventral tegmental area (VTA), a brain structure involved in reinforcement, arousal and processing of reward-driven behavior, can dramatically affect CA1-plasticity, we also investigated how VTA-stimulation does influence stress-altered plasticity in the CA1.
fEPSPs were recorded from commissural path-CA1 apical dendrite synapses in conscious rats. After baseline recordings, rats were subjected to a swim episode 15 min before or after or 4 h after (delayed stress) strong tetanization of the contralateral CA3. In experiments with VTA stimulation, the latter was conducted shortly before LTP induction or swimming. Our results revealed that swim stress alone transiently (<3h) depressed baseline values of the fEPSP slope. Swimming close to the time point of tetanization transformed LTP into LTD, whereas delayed stress depotentiated LTP to the baseline values. VTA stimulation before the swim episode converted the short-term depression or the depotentiation induced by delayed stress into LTD. Altered CA1 plasticity was reset to baseline when VTA was activated prior to tetanization followed by swim. Thus, the timing of the swim episode in relation to tetanization as well as VTA-activation within distinct times around electrophysiological or behavioral procedures is important to determine the associative plasticity outcome in the CA1. To further investigate direct synaptic events we will use a double recording technique (fEPSP and population spike) and plan to implement a weak tetanization protocol to study possible processes of LTP-reinforcement by swim and/or VTA-activation in the CA1.

P03: Transgenic expression of the serine/threonine kinase Ndr2 increases hippocampal mossy fibre density and enhances open field exploration in mice

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The serine/threonine kinase Ndr2 is critically involved in actin-mediated cell growth and morphogenesis. We could previously show that Ndr2 has a regulatory role in neurite outgrowth of transfected pheochromocytoma cells (PC12), as well as acutely transfected hippocampal primary neurons. In order to further investigate neuronal functions of Ndr2 in vivo we generated transgenic mice which conditionally overexpress an EGFP-tagged Ndr2 under the control of the promoter for calcium/calmodulin dependent kinase IIa (Camk IIa), using a CRE-recombinase/stopflox system. Two independent lines of transgenic mice were obtained which express the fusion protein at different levels in the mouse forebrain. Animals are viable and without apparent major morphological or behavioural abnormalities. However, analysis of hippocampal mossy fibers using the Timm staining method revealed an increased density of the infrapyramidal mossy fibre band in the ventral hippocampus of the mutant mice. This morphological change appears to be functionally relevant, as Ndr2 transgenic mice furthermore displayed enhancement of mossy fibre-dependent exploratory behaviour in an open field. Previously, homologs of the mammalian serine/threonine kinase Ndr2 in D. melanogaster (Tricornered) and C. elegans (SAX-1 and SAX-2) have been shown to regulate dendritic branching and tiling of sensory neurons. Our data now demonstrate that Ndr2 is capable of modifying axonal outgrowth and hippocampus-dependent behaviour in mammals.

P04: NCAM knock out mice: a model for autistic features?

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Autism is a neurodevelopmental disorder, characterized by impaired social interaction, disturbed communication and restricted, stereotyped or repetitive behavioral patterns. Autistic disorders are often accompanied by cognitive difficulties, attentional problems, or emotional disturbances. Based on genetic and functional studies, disturbances of cell recognition molecule function have been implicated in the development of autism and are thought to contribute to a disturbed neurocircuit connectivity in the autisic brain, in particular to abnormal amygdala and hippocampal growth and cytoarchitecture. The neural cell adhesion molecule (NCAM) is known to mediate cell-cell- and cell-matrix-interactions in the central nervous system and to be critically involved in various types of adaptive behaviors, including anxiety-like and aggressive behavior as well as the amygdala-mediated modulation of hippocampus-dependent memory formation Here we investigate species-specific innate social behavior by assessment of nest building and social interaction in mice with targeted disruption of the NCAM gene (NCAM-/- mice). We observed that, with no apparent deficit in thermoregulatory functioning, NCAM-/- mice continuously collected smaller amounts of nest building material than their wild type littermates and built nests of poorer quality. Moreover, NCAM-/- mice showed a mild dissocial phenotype spending less time near an unfamiliar mouse in a long-term social interaction experiment. Cognitive functions in a Morris Water Maze paradigm were not disturbed and NCAM-/- mice did not display restrictive or repetitive behavior in a reversal task. Together with the previously described increased anxiety-like and aggressive behavior, the mild social impairments together with normal cognitive function and flexibility suggest that NCAM mutant mice may be used to model symptoms of a high functioning autism with emotional comorbidity.

P05: Early neuronal dysfunction by amyloid β oligomers depends on activation of NR2B-containing NMDA receptors

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Several studies indicate that NMDA receptor signaling is involved in Aβ oligomer mediated impairment of neuronal function and morphology. Utilizing primary neuronal cell culture and hippocampal slices from rat and mouse, we found that Aβ oligomer administration readily impairs long-term potentiation, reduces baseline synaptic transmission, decreases neuronal spontaneous network activity and induces retraction of synaptic contacts long before major cytotoxic effects are visible. Interestingly, all these effects can be blocked with the NR2B containing NMDA-receptor antagonist ifenprodil or Ro 25,-6981 suggesting that activation of downstream effectors of these receptors is involved in early detrimental actions of Aβ oligomers. In line we found that Jacob, a messenger that can couple extrasynaptic NMDA-receptor activity to CREB dephosphorylation, accumulates in the nucleus after Aβ oligomer administration and that the nuclear accumulation of Jacob can be blocked by a simultaneous application of ifenprodil. We conclude that Aβ oligomers induce early neuronal dysfunction mainly by activation of NR2B containing NMDA-receptors.

P06: Towards a network of synaptic protein interactions as a basis for dynamic modeling of synaptic signaling pathways

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Synapses are specialized cell-cell contacts between neurons of the central nervous system, which are characterized by highly specific networks of proteins at the synaptic membranes. The cytomatrix at the active zone (CAZ) is organizing at the presynaptic side the apparatus for the regulated release of transmitters. At the postsynaptic side the postsynaptic density (PSD) represents the machinery for detection, integration and transduction of the transmitter signal. The pre- and postsynaptic protein networks are the substrates for synaptic plasticity and are functionally regulated in their composition and modification of their components. These protein networks will be investigated by application of methods of bioinformatics and systems biology. The first step is the construction of a static interactom, i.e. the representation of the protein – interactions without considering the degree of modification. In a next step all static interactions will be replaced by ‘rules’, which describe the preconditions of a specific interaction. At this step it will be possible to construct dynamic protein networks for modeling of temporal processes of e.g. signal transduction. An additional aim is the detection of unknown signaling proteins by simulations and therefore to propose specific experiments. Background information is provided by a manually curated MySQL-database and is confirmed by a team of specialists. For an easy retrieval of information, the databases will be completed with a user friendly interface and network visualization software. The visualization of the interactions of pre- and postsynaptic proteins is based on the prefuse toolkit (http://prefuse.org) and implements several layouts. The layout can be exported as an image in common formats. The dynamic visualization can be manually manipulated by changing the positions of the proteins, by zooming or by changing edge lengths or node labelings. The software is on an early stage and further modules will implement user-editing functionality and visualization of additional information such as images and 3D-structures of proteins. Only interactions between two proteins are coded in the database, interactions of more than two proteins or of proteins and other molecules like DNA/RNA are not implemented until now. Therefore the database will be enhanced with more information like protein complexes (interactions with more than two proteins), RNA/DNA-protein interactions and localizations of the protein within the brain. As a last step, the database will be completed with interaction properties, which describe the preconditions of a specific interaction. With this information it will be possible to construct dynamic protein networks for modeling of temporal process like signal cascades.

P07: Histone Modifications in Frontal Cortex of Neonatal Maternally Separated Mice

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Histones are subject to a wide variety of posttranslational modifications including acetylation, methylation and phosphorylation, which are regulated by specific enzymes. Overall, posttranslational modifications of histones create an epigenetic mechanism for the regulation of a variety of normal and disease-related processes. The aim of the present study was to clarify if neuronal network adaptations to early stress experience which have been described previously are correlated to specific histone modifications. We established the technique of Chromatin immunoprecipitation (ChIP) to look into the details of histone-DNA interactions and the consequences of experience-induced histone modifications for gene expression in the prefrontal cortex. The present study concentrated on differences in the acetylation of histone H4 (Ac-H4) and histone H3 (Ac-H3) between maternally separated and control mice. After ChIP with Ac-H3 and Ac-H4 precipitated DNA was used for qPCR. We focussed on the promoter regions of Arg3.1/Arc or Egr1. It was observed that both Arg3.1/Arc and Egr1 in maternally separated animals were significantly elevated after ChIP with Ac-H3 than these in control, whereas only a trend towards increase was observed after ChIP with Ac-H4. The results indicate that the previous described neuronal alterations after stress are presumably correlated to the activation of Arc and Egr1 transcription, which is regulated by histone H3 acetylation. Acknowledgement:The work was supported by Land Sachsen-Anhalt, EU-Strukturfonds 2007-2013.

P08: Superior memorizers recruit a small left lateralized network of brain areas when using the method of loci for encoding

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The method of loci may be useful to prevent the loss of cognitive abilities during aging and neurodegenerative diseases. The consequences of excessive training on neural plasticity, however, is not well studied. We examined a group of superior memorizers who employ this memory-technique. So far, only one brain-imaging study has been performed on this topic (Maguire et al., 2003 Nat Neurosci, 6, p90) and the main finding was that such superior memory is not due to structural brain differences but is associated with only a few brain areas that are more strongly engaged in memory tasks. The aim of our study was to replicate such findings and differentiate fMRI activation that occurs during encoding and recall of a large number of items. 7 superior memorizers and 7 controls were scanned at 3 Tesla. 695 volumes were acquired in 23:10 min using standard EPI. Each of the 8 experimental blocks consisted of 4 conditions. 1. Endode: 40 digits were presented for 60s and the subjects had to memorize as many items as possible. 2. Attend: A similar matrix was presented for 20 s and the subjects had to indicate whether each digit was even and in sum marked by two dashes below and above. This condition was used to stop the subjects from encoding and controlled for both the visual input and the attentional demand. 3. Recall: Verbally recall as many digits as possible within 60 s. 4. Rest: Recite the alphabet within 30 s. Data were analyzed with BrainVoyager using 3D-motion correction, high-pass filtering, spatial smoothing (Gaussian filter, FWHM=4mm), a p-value of < 0.01 (Bonferoni-corrected), and min. cluster size=8. Brain regions specifically involved in the encoding by superior memorizers were left lateralized secondary visual areas (BA 18, 19), left medial superior parietal cortex (BA 7), left middle temporal gyrus (BA 39), bilateral retrosplenial cortex (BA 30), and bilateral posterior parahippocampal gyrus. However, none of these regions were specifically involved during the recall condition. Instead we found the right premotor cortex and the anterior superior temporal gyrus (predominantly on the left) to be significantly active in the superior memorizers. We suggest that the involvement of the visual areas in the encoding condition reflects the strategy of the superior memorizers to translate the digits into visual objects. These object representations are then put on different salient locations of a well known route. This would explain the activation of the parahippocampal gyrus and the retrosplenial cortex which are involved in mental navigation (Epstein, 2008, Trends Cogn Sci, 12, p388; Ghaem et al., 1997 Neuroreport, 8, p739). A left medial superior parietal cortex (BA 7) activity was also described by Maguire et al. who suggested an involvement in spatial memory and navigation. We interpret the left dominance in most of the active brain areas during encoding as a specialization of the left hemisphere in sequential processing.

P09: Are direct primary sensory cortex connections also made for learning and memory?

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During the last years it has become increasingly apparent that primary sensory cortices, like the primary auditory cortex (AI), are not purely unisensory but also process complex information from other sensory modalities as well as non-sensory information.
Here, we review our anatomical work (basically neuronal tract tracing) on the connections of the auditory cortex in a small rodent, the Mongolian gerbil (Meriones unguiculatus), a common animal model in auditory and learning research. In particular we will show that AI has multiple direct connections with “higher order” associative brain areas, like the prefrontal cortex and amygdala, as well as with neuromodulatory structures, like the ventral tegmental area and nucleus basalis, which sum up to approximately 6% of the neuronal inputs into AI. The laminar patterns of axonal terminations as well as cells of origin in AI point to the specific feedforward / bottom-up and feedback / top-down nature of these connections.
In summary, most connections are suitable to mediate multimodal integration processes observed at the level of AI and, in turn, enable AI to influence other sensory and non-sensory systems at several cortical and subcortical levels as required for the formation of associations as well as learning and memory processes.

P10: The impact of sex, diurnal phase and conditioned stimulus modality on infant and adult two-way active avoidance learning in rats

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A growing body of evidence supports the hypothesis that juvenile cognitive training shapes neural networks and behavior, and thereby determines the adult´s capacity for learning and memory. In particular, we have shown that infant rats are unable to learn an active avoidance strategy in a two-way active avoidance (TWA) task, but nevertheless learn the same learning task faster as adults, indicating that a memory trace was formed in the infant rats, which most likely is recruited during adult training. The objective of the present study was to test the hypothesis that the learning impairment of infant rats might at least in part result from indadequate training conditions. TWA learning was assessed in i.) male and female rats trained ii.) as infants or adults during iii.) the light- or dark-phase using iv.) a tone or light as the conditioned stimulus (CS). Furthermore, v.) rats pre-trained as infants were re-trained as adults to examine the impact of the different training parameters on improved adult learning. Our results revealed that i.) there was no main effect of sex, ii.) infants were poor learners compared with adults. Furthermore, irrespective of sex or age learning performance was improved iii.) during the dark-phase, and iv.) but was not affected by CS modality. Additionally, v.) pre-training accelerated avoidance learning most pronounced in females which were pre-trained during the dark-phase with either light or tone as CS. Taken together, our data clearly show that TWA performance in infant and adult rats is sensitive to the diurnal rhythm. In addition, we demonstrated that the impaired avoidance learning in infants is not the result of inadequate training parameters, but might be related to the immaturity of the brain circuits and an insufficient recruitment of brain regions which are essential to learn an active avoidance strategy. Supported by the German Science Foundation (SFB 779) and Center for Behavioral Brain Sciences (CBBS 3804 B).

P11: Ontogeny of two-way active avoidance behavior: learning capacity in infant and adolescent rats may be determined by differential metabolic recruitment of prefrontal and limbic regions

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Infant rats are not able to generate two-way active avoidance (TWA) behavior during repeated training in the shuttle-box. However, these animals obviously deposit a certain “memory trace” during early training as they learn much faster than their naive (not pre-trained) littermates when re-trained in adulthood. We hypothesize that the behavioral differences between infant (insufficient TWA performance) and adolescent (sufficient TWA performance) rats are mirrored by differential metabolic recruitment of brain regions involved in the task. Mapping 2-Fluoro-deoxy-glucose utilization, we compared the metabolic activity in 39 brain regions in infant (P17-P21) and adolescent (P38-P42) rats during acquisition and retrieval of a TWA task. Principal component analysis revealed 1) a cognitive/sensory-motor, 2) an emotional-autonomic and 3) a modulatory component, which contributed to the variance of the metabolic activity. Inter-regional correlation analysis of the metabolic activity of the brain areas loading to the components revealed an increased degree of correlation with repeated training. During retrieval, the infant rats displayed a correlation pattern resembling that of adolescent animals during acquisition, which implies that their brains are still “under acquisition” after repeated training. Analysis of behavioral parameters during adolescence revealed a negative correlation of avoidance performance with cortico-limbic, hippocampal, modulatory and sensory-motor brain regions implying that learned tasks require less energy. In contrast, brain activity in infant rats was not correlated with avoidances but negatively correlated with the total shock exposure (adding up escapes and failures) in the hippocampus, extended amygdala and PAG. This indicates that the aversive stimulus suppresses activation of the brain regions required for learning the avoidance strategy in infant rats. Taken together, we conclude that especially the mature functional connectivity of the extended amygdala with prefrontal areas and modulatory brain stem regions is essential for the translation of acquired information into behavioral output during TWA learning.

P12: Influence of electrical stimulation of the ventral tegmental area on field potentials in hippocampal CA1 of freely moving rats

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The prolonged maintenance of hippocampal long-term potentiation (LTP), i.e. the protein synthesis-dependent phase beyond 4-6 h (L-LTP) requires heterosynaptic, late-associative events during LTP induction. We had shown in hippocampal slices in vitro, that L-LTP requires dopaminergic D1/D5-receptor activation in a synergistic interaction with NMDA-receptor function within a distinct time window (Frey at al. 1990, 1991, 1993; Frey and Morris, 1998). The main source for this dopaminergic input to area CA1 is the ventral tegmental area (VTA), a heterogeneous group of dopaminergic cells and a major component of the mesolimbic dopamine system. Recently we had shown, that high-frequency stimulation of the VTA caused a delayed-onset potentiation of the recorded field-EPSP and population spike (POP) in CA1 in response to test stimulation of the contralateral CA3 in freely moving animals. This delayed-onset potentiation was dependent on the synergistic activation of both the glutamatergic and dopaminergic inputs, because paused glutamatergic test stimulation abolished this potentiation. These results again supported our findings in hippocampal slices in vitro. We were now interested to study if this delayed-onset potentiation in vivo was also protein synthesis-dependent. References: Frey et al., Brain Res. 522 (1990), Frey et al. Neurosci. Lett. 129 (1991), Frey et al. Science 260 (1993), Frey & Morris TINS 21(1998)
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P13: Infant avoidance training blocks adult avoidance learning in mice

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Cognitive training during early childhood plays an important role in shaping neural circuits and learning capacity in adulthood. We have shown in rats that preweaning avoidance training in a two-way active avoidance (TWA) task accelerated avoidance learning in adulthood compared to non pre-trained adults. The aim of the present study was to replicate these studies in mice (C57BL/6), and specifically examine the i) age-dependency of TWA learning, and ii) the impact of infant pre-training on adult learning. In search for epigenetic mechanisms underlying avoidance learning in mice we examined the expression of phosphoacetylated histone H3 positive neurons [P(Ser10-Ac(Lys14)-H3+] in the dentate gyrus and amygdala immunohistochemically labelled serial brain sections.
We found that i) infant mice at the age of 3 weeks showed attenuated avoidance performance compared to adults; ii) mice pre-trained as infants completely failed to learn an active avoidance strategy in adulthood as opposed to non pretrainied controls, iii) the number of P(Ser10)-Ac(Lys14)-H3+ neurons in the dentate gyrus was lower in infant than in adult brains, and iv) there is no difference of H3-labelled neurons between trained and naive mice in all age groups. In summary, these data revealed opposite behavioral results compared to those previously obtained in rats: Pre-training in young rats accelerates adult avoidance learning, whereas pretraining in infant mice completely blocks avoidance learning in adulthood. The different cognitive outcome in the two species indicates that different epigenetic mechanisms and neuronal reorganization of learning-relevant brain circuits are involved, which have to be identified in future studies. Supported by the German Science Foundation (SFB 779) and Center for Behavioral Brain Sciences (CBBS 3804 B).

P14: Spatial and temporal dynamics of newly synthesized proteins in developing neural cells

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Dynamic protein synthesis in neurons is an essential prerequisite for both synaptic maintenance and modification ("synaptic plasticity"). This process is tightly regulated and occurs in the somata as well as in distal protrusions of these cells. Besides the rapidly growing amount of evidences that local translation is one of the key events for these processes, it is unclear if there is a role for temporally and spatially regulated protein synthesis in neurons and astrocytes during development as well. For that purpose we apply the recently developed BONCAT-(bioorthogonal non-canonical amino acid tagging) technology, followed by affinity purification and two-dimensional tandem mass spectrometry to the identification of newly synthesized proteins in developing neural cultures and in the developing rat brain. BONCAT endows newly synthesized proteins with a novel chemical functionality and is based on the co-translational introduction of azide groups into proteins followed by chemo-selective tagging of azide-labelled proteins with an alkyne-affinity tag. For our experiments the non-canonical azide-bearing amino acid Azidohomoalanine (AHA) as a surrogate for methionine is used. In combination with leucine-based mass tagging, candidates can be immediately and confidently validated. BONCAT identified proteomes provide a comprehensive picture about the temporal and spatial characteristics of newly synthesized proteomes in sub-cellular biochemical fractions from the developing rat brain as well as in primary neural cell cultures in vitro. In the present study we analysed and identified newly synthesized proteins in synaptosomes, prepared from AHA-labelled cortical primary cultures, as well as in isolated synaptoneurosomes (SNS) prepared from dissected rat brains at different developmental stages. SNS are translational active, biochemical fractions enriched in synaptic specialisations and contain all components of the protein synthesis machinery. Our electron microscopy investigations show synaptic structures in the immediate vicinity of astroglial end feet indicating intact tripartite synapses, which enable the simultaneous acquisition of multiple proteomes from different cellular origins. First results of our analysis suggest that local protein synthesis is not exclusively restricted to dendritic structures and to mature systems, but also might occur during brain development and in axonal terminals.

P15: Frequency-dependent modulation of Spike Timing-Dependent Plasticity by brain-derived neurotrophic factor

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Long-term potentiation (LTP) and long-term depression (LTD) are considered as neuronal substrates for learning and memory. Conventionally, LTP is induced by high frequency stimulation or by theta-burst stimulation and is critically dependent on the presence of “brain-derived neurotrophic factor” (BDNF). To clarify a possible role of BDNF in LTP under more moderate stimulation conditions, we here focused on a low frequency induction protocol, which is called spike timing-dependent plasticity (STDP). This type of plasticity can be induced by precisely timed pairing of pre- and postsynaptic action potentials (APs).
In an attempt to establish STDP, we used different low frequency pairing protocols with different numbers of postsynaptic stimuli (one presynaptically induced excitatory postsynaptic potential (EPSP) and one or two postsynaptic APs) in acute hippocampal slices of P15-P20 rats. Short positive pairings at +15 ms between pre- and postsynaptic activation lead to a significant timing-dependent LTP (t-LTP) compared to unpaired controls (e.g. pairing at +15ms with 1 EPSP/1 AP: 1.71±0.1 of initial values; control: 0.98±0.1). Pairings with negative intervals lead to a timing-dependent LTD (e.g. t-LTD at -15ms with 1 EPSP/1 AP: 0.85±0.1 compared to control: 0.98±0.1). The t-LTP induced by 1 EPSP/1 AP pairings at short positive pairings was blocked in the presence of DL-APV during recordings (1.15±0.15 compared to 1.78±0.12), therefore indicating a dependence of t-LTP on the activation of NMDA receptors. In order to investigate the mechanism of LTP expression employed by our STDP paradigm, we studied changes in the paired pulse ratio (PPR), and analyzed changes of spontaneous miniature currents before and after STDP induction. According to these experiments, expression of STDP is a highly cell-specific phenomenon and involves pre- and/or postsynaptic mechanisms in individual cells. Using the Trk kinase inhibitor k252a, we investigated involvement of BDNF/TrkB signaling in our STDP paradigm. Preliminary results suggest a frequency dependent involvement of BDNF in STDP induction: a low BDNF/TrkB sensitivity of the 1 EPSP/1 AP pairing paradigm (100 repeats) was observed (t-LTP in the presence of k252a at +10ms: 1.64±0.4 vs. 1.74±0.1 (control)). When using a stronger and more efficient paradigm for STDP induction (1 EPSP/2 AP pairings, 50 repeats), blocking BDNF/TrkB signaling seemed to have a larger impact on the efficiency of STDP induction (k252a at 10ms: 1.38±0.3 vs. 2.00±0.4 (control)). To test our hypothesis, we are currently investigating a further STDP protocol with 4 postsynaptic stimuli (1 EPSP/4 AP pairings, 25 repeats). From these data we conclude that the expression mechanism of STDP in our recordings is a highly cell-specific phenomenon. We also suggest an involvement of BDNF in hippocampal STDP which is dependent on a threshold level of stimuli during pairing.
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P16: Impaired long-term plasticity at thalamic input synapses to projection neurons of the lateral amygdala in heterozygous BDNF knockout mice

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Brain-derived neurotrophic factor (BDNF) has been shown previously to play important roles in neuronal survival, synaptogenesis, and in activity-dependent synaptic plasticity, as e.g. long-term potentiation (LTP). In the amygdala, LTP-like associative processes correlate with cued fear conditioning. Recent data suggest that signalling cascades downstream of the BDNF/NT-4/5 specific TrkB tyrosine kinase receptor modulate fear learning as well as amygdala synaptic plasticity. However, the underlying cellular mechanisms for BDNF-dependent LTP and learning at the level of individual neurons still remain elusive. We therefore used a BDNF heterozygous knockout mouse model (BDNF+/-) to characterize LTP and basal properties of projection neurones out of the lateral amygdala (LA) using the whole cell patch clamp technique in an in vitro slice preparation. When stimulating the cortical input, LTP of excitatory postsynaptic currents (EPSCs) could be induced reliably in LA neurons, by a protocol pairing postsynaptic depolarisation and presynaptic stimulation. LTP was not significantly different between BDNF+/- mice and wildtype littermates. In contrast, LTP was significantly impaired in neurons from BDNF+/- mice when potentiating the thalamic input (BDNF+/-: 104.0 ± 5.7 % of initial EPSC values; WT: 132.5 ± 7.3 %). This LTP was sensitive to blockade of NMDA receptors. Reduced expression of BDNF did not affect the intrinsic membrane properties of LA projection neurons, as input resistance, resting membrane potential, spike threshold, half width, mean frequency and adaptation did not show significant alterations between the two experimental groups. In addition, presynaptic glutamate release was unchanged, as documented by a lack of effect on paired pulse ratios and synaptic fatigue. Possible synaptic mechanisms underlying the observed BDNF-dependent LTP will be discussed. Supported by the Deutsche Forschungsgemeinschaft SFB 779, TP B6.

P17: How outcome expectations organize learned behaviour in larval Drosophila

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Drosophila larvae combine a numerically simple brain, a correspondingly moderate behavioural complexity and the availability of a rich toolbox for transgenic manipulation. This makes them attractive as a study case when trying to achieve a circuit-level understanding of behaviour organization. From a series of behavioural experiments, we here suggest a circuitry of chemosensory processing, odour-tastant memory trace formation and the 'decision' process to behaviourally express these memory traces- or not. The model incorporates statements about the neuronal organization of innate versus conditioned chemosensory behaviour, and the kinds of interaction between olfactory and gustatory pathways during the establishment and behavioural expression of odour-tastant memory traces. It in particular suggests that innate olfactory behaviour is responsive in nature, whereas conditioned olfactory behaviour is captured better when seen as an action in pursuit of its outcome. It incorporates the available neuroanatomical and behavioural data and thus should be useful as scaffold for the ongoing investigations of the chemo-behavioural system in larval Drosophila.

P18: Bassoon and Piccolo interact with RIM-binding proteins and thereby regulate the localization of presynaptic calcium channels

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Synaptic vesicle exocytosis is triggered by calcium influx through voltage-dependent calcium channels (VDCCs) and is restricted to a specific region of the presynaptic membrane: the active zone (AZ). VDCCs, mainly Cav2.1 and Cav2.2, are clustered at the AZ in the vicinity of docked synaptic vesicles (SVs). This co-localization is thought to be essential for the efficacy of neurotransmitter release in response to calcium influx. To date, it is not clear which molecular interactions underlie such precise spatial coordination. Here we report on a newly discovered interaction of core components of the presynaptic AZ – Bassoon and Piccolo – with RIM binding proteins (RBPs), which in turn interact with RIMs and VDCCs and can serve as linkers between these channels and the priming-fusion apparatus for SVs. In yeast two-hybrid assays, a specific PXXP motif of Bassoon and the corresponding sequence of Piccolo were identified as regions interacting with all three SH3 domains of RBPs. The interaction was confirmed in heterologous expression systems and using Surface Plasmon Resonance (SPR) technology as well as by co-immunoprecipitation of Bassoon and RBP2 complex from rat brain homogenate. Using SPR we measured relative affinities of distinct SH3 domains of RBPs to Bassoon, Piccolo, RIM1 and Cav2.2 and found that particular SH3 domains posses differential binding preferences suggesting that RBPs might functionally couple Bassoon and VDCCs. In agreement with this assumption, we demonstrated the co-localization of RBP2 with Bassoon, CaV2.1 and CaV2.2 at presynaptic terminals of primary hippocampal neurons. In neurons from Bassoon-deficient mice, the synaptic localization of CaV2.1 and RBP2, but not of CaV2.2 or Synaptophysin was perturbed suggesting that Bassoon might be specifically involved in targeting or retention of RBP2 and CaV2.1 to synaptic sites. This hypothesis was further supported by observation that over-expression of GFP-Bsn construct, but not its RBP-binding deficient mutant caused an increase in synaptic recruitment of CaV2.1 and RBP2 but not of CaV2.2 or Piccolo. These findings indicate RBPs as new interaction partners for Bassoon and Piccolo. Moreover, they provide new insights on the mechanisms underlying the proper VDCC localization in the presynaptic membrane.

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P19: Early stress experiences prevent emotional reinforcement of hippocampal long-term potentiation in adult male rats: active extinction of traumatic memories as a disease-protective mechanism?

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Maternal separation (MS) paradigms are well established animal models to analyze stress related brain disorders. In order to study the effects of MS on hippocampal long-term potentiation (LTP), which is considered as a cellular model of memory formation, a repeated separation paradigm that male Wistar rats were deprived from their dams for everyday 6 hours from postnatal day (PND) 14 to PND 16 was used and the animals were tested for LTP in the dentate gyrus (DG) at adolescence (10 weeks old). Here, we show that the foregoing separation impairs the emotional LTP-reinforcement (transferring early-LTP into protein-synthesis dependent late-LTP) induced by exposing the animals to a 10-min. elevated-platform-stress (EPS) immediately after the high frequency stimulation (HFS) triggering early-LTP in DG. In order to reveal possible involvements of stress related steroid hormones on the observed LTP-modulation, we studied the expression patterns for a series of steroid hormone receptors (that act as transcription factors), hormones and neurotrophic factors after stress in comparison to non-deprived rats. EPS strongly elevates the level of corticosterone 15 min post-stress with no differences between groups. Hippocampal mRNA of the corticosterone binding mineralocorticoid receptor (MR), whose activation is proved to be necessary for emotional LTP-reinforcement, is upregulated 1h after stress in control rats, whereas deprived rats show no significant increase of MR expression after adult stress. Similar differences appeared in the expression of androgen receptor (AR) and aromatase mRNA. In contrast, estrogen receptors (ER) mRNA is expressed more highly in deprived rats than controls 1h after stress. Furthermore, deprived rats show an increased hippocampal BDNF level 24h after HFS and stress as compared to controls. We hypothesize an active extinction of traumatic memories in adult, early deprived rats induced by steroid-BDNF interactions to protect from further traumatic memory overload. The observed differences in gene expression and possibly protein-synthesis might be due to epigenetic chromatin modifications.

P20: Cell-selective visualization of newly synthesized proteomes in mammalian primary co-cultures and in Drosophila melanogaster

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Dynamic protein synthesis is a common feature of cells and cellular networks to respond to changes in their environment, or to alterations in molecular communication itself.
Here we introduce an approach to track newly synthesized proteins in selected cells in primary neural co-cultures and in larvae of Drosophila melanogaster, extending the previously reported technologies BONCAT (bioorthogonal amino acid tagging) and FUNCAT (fluorescent non-canonical amino acid tagging). Metabolic labeling of newly synthesized proteins is based on the non-canonical amino acid Azidonorleucine (ANL), which is incorporated into proteins upon expression of a mutated methionine tRNA synthetase (MetRS). Replacement of a single leucine residue by glycine (LtoG) in the binding pocket of the enzyme enables the efficient activation of ANL and its subsequent incorporation into proteins of cells expressing LtoG-MetRS, thus endowing the proteins with novel azide functionality. Employing copper-catalyzed [3+2]-azide-alkyne-cycloaddition ('click chemistry'), the reactive azide group of ANL is covalently coupled either to a fluorescent alkyne-tag (FUNCAT) or to an alkyne-bearing affinity tag (BONCAT). While FUNCAT is aimed at visualizing ANL incorporation within individual cells, BONCAT provides a means to identify labeled proteins, e.g. by Western Blot– or mass spectrometric analyses. Based on both reactions we show that expression of LtoG-MetRS under the control of the GFAP-promoter leads to the incorporation of ANL into the proteome of astrocytes but not into the proteome of co-cultured neurons. Targeted expression of LtoG-MetRS thus allows to distinguish glial and neuronal proteomes within in a co-culture system. To further assess the in vivo versatility of this technology, we introduced an inducible transgene encoding LtoG-MetRS fused to GFP (UAS-LtoG-MetRS-GFP) into the genome of Drosophila and expressed the mutated enzyme in neurons, glia or muscle cells, respectively. Cells expressing LtoG-MetRS-GFP were found to use food-supplied ANL as a surrogate for methionine during translation, and hence showed extensive signals representing newly synthesized proteins. Incorporation of ANL was neither detected in cells of the same animal that lacks expression of LtoG-MetRS nor in animals expressing wild type MetRS-GFP. These findings document for the first time, that it is possible (i) to incorporate ANL into newly synthesized proteins in an in vivo-system and that it is possible (ii) to detect these proteins either biochemically (BONCAT) or immunohistochemically (FUNCAT). Notably, flies, subjected to ANL-incorporation in glia or neurons throughout development remain viable and fertile. Using this cell-select labeling we aim to visualize neuronal and glial proteome dynamics in their native cellular context, thereby deepening our understanding of the molecular and systemic aspects of the neuron-glia partnership.

P21: Mapping Fucosylated Synaptic Proteins with Aleuria Aurantia Lectin and Click Chemistry

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The brain is a highly complex entity comprising a variety of proteins with posttranslational modifications, such as glycosylation. Fucosylated carbohydrate structures in the brain are crucial for neuronal plasticity. Plasticity phenomena like hippocampal long-term potentiation (LTP) and memory formation are accompanied by a transient increase in the incorporation of fucose into membrane glycoproteins. Interestingly, inhibition of protein fucosylation does not interfere with LTP induction or memory acquisition, but prevents specifically the long-term maintenance of LTP and memory. The mechanisms underlying the particular importance of protein fucosylation for phenomena of long-term synaptic plasticity as well as the identity of synaptic fucosylated proteins are largely unknown. Therefore, as a first step to better understand the role of protein fucosylation in the context of neuronal plasticity, we attempted to identify fucosylated synaptic proteins. In the present study, the fucose-specific lectin from Aleuria aurantia (AAL) was used to investigate the distribution of fucose-containing carbohydrate moieties in rat brain. We found strong AAL staining of membrane structures especially in synaptic neuropil regions. To identify fucosylated synaptic proteins, extracts from synaptic junctions were analysed either in a targeted approach using immunoprecipitations and lectin blotting or in an unbiased approach using tandem AAL-affinity chromatography with subsequent identification of glycopeptides by LC-MS/MS. For the targeted approach we focused on proteins previously implicated in neuroplasticity, i.e. neurotransmitter receptors, cell adhesion molecules, extracellular matrix proteins, voltage gated potassium and calcium channels, growth factor receptors and ligand-gated ion channels. We identified 19 proteins that were previously not known to be fucosylated. In addition we use an azide-labelled fucose derivative to specifically label and identify de novo fucosylated proteins in primary cortical cultures under basal and NMDA-elicited synaptic activation. Supported as IfN Special Project (WT, KHS, DCD), DFG SFB 779 (TK, WT), EU Structural Funds 2007-2013 (WT, KHS) and the DFG Emmy Noether Program (DCD).

P22: Electrical perforant pathway stimulation triggers enhanced BOLD responses in various target regions of the hippocampus subsequent the same stimulus was used as a conditioned stimulus for an active avoidance learning

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Functional magnetic resonance imaging (fMRI) and electrophysiology was used to monitor simultaneously blood oxygen level dependent (BOLD) signals in the entire rat brain and neuronal activity in the dentate gyrus triggered by repetitive electrical stimulation of the right perforant pathway. Elicited responses were measured before and after the stimulus was used as conditioned stimulus for an active avoidance task. One day after acquisition of the avoidance reaction the stimulus induced an increased granular cell spiking in the right dentate gyrus, stronger BOLD responses in the dentate gyrus, and additional BOLD responses in the nucleus accumbens, the agranular insular cortex, the septum, the anterior cingulate cortex, and motor cortex. Neither mere repetitive stimulations nor doubling the stimulation intensity could trigger similar strong BOLD responses in the dentate gyrus and equal BOLD responses in the additional regions. Thus, our findings visualize a different processing of an identical stimulus depending on its behavioral relevance.

P23: Activity-dependent remodelling of the presynaptic cytomatrix at the active zone

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Excessive excitation or inhibition induces compensatory changes in efficacy of synaptic transmission. This homeostatic plasticity serves to keep network activity within a physiologically meaningful frame – a prerequisite for effective learning-induced plasticity. Homeostatic adaptations are of tremendous importance during development of the nervous system, in experience-dependent plasticity and under pathological conditions. They are achieved by modulation of the presynaptic neurotransmitter release machinery and by changes in neurotransmitter sensing by postsynaptic elements. Proteins of the presynaptic cytomatrix at the active zone (CAZ) are important modulators of release efficiency during Hebbians' plasticity, however, to date their role in homeostatic plasticity was neglected. In this study we have investigated whether and how the altered synaptic network activity influences the molecular composition of the presynaptic active zone (AZ). We used primary cultures of cortical neurons as a convenient model system allowing pharmacological manipulations and we could demonstrate that prolonged network activity deprivation induces significant down-regulation of the expression levels of CAZ-specific proteins Bassoon, Piccolo, Munc13, RIMs and Liprin-alphas, as well as, of the presynaptic scaffolding protein Synapsin. The same condition did not alter expression levels of synaptic vesicle proteins such as SV2B and Synaptophysin and SNARE proteins Syntaxins. The observed activity-dependent remodeling of the AZ was reversible when activity block was removed indicating that our observations are of physiological relevance. Looking at the level of single synapses we detected a depletion of synaptic CAZ from a fraction of synaptic sites and a remarkable redistribution of RIM. The immunoreactivity of RIM at individual synapses correlated well with their activity, as visualized by sponataneous activity-induced uptake of an antibody against the luminal domain of Synaptotagmin. Moreover we observed significant increase of synaptic immunoreactivity for high current-conducting Cav2.1 in activity deprived neurons. We propose that the redistribution of RIM together with upregulation of Cav2.1 might represent the molecular mechanism underlying the increase of release probabilities induced by prolonged silencing of network activity. Supported by the DFG (SFB 779, GRK 1167, HE3604/2-1) and CBBS (European Commission [EFRE] and Land Saxony-Anhalt).

P24: Auditory gating in the striatum and auditory cortex: Dynamics of cortical and striatal interactions and the effects of discrimination learning

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In this study we investigated how auditory information is processed in the ventral striatum. We recorded local field potentials in chronically implanted Mongolian gerbils to study basal interaction between auditory cortex and the ventral striatum during auditory processing, particularly using the sensory gating paradigm. Sensory gating is a process by which a sensory event modulates neuronal signals of subsequent sensory stimuli of the same or different sensory modality. Gating could be a filter mechanism preventing the brain from an overflow of distracting information. Functionally, the striatum is also thought to be a reward evaluating structure. Therefore we were interested in how auditory processing and gating is altered once an auditory stimulus is associated with meaning. To investigate learning effects, animals were trained in a Go/NoGo task using trains of frequency-modulated tones. Neuronal responses were compared before and after the training. Even today it is not clear if auditory evoked potential gating is transmitted from one non-lemniscal site to another or if inhibition is carried out locally. To elucidate this question we additionally recorded and analyzed multi-units in both areas simultaneously. Additionally, we were interested in whether neural interactions between auditory cortex and striatum of the ongoing activity is influenced by the discrimination learning procedure. Therefore we performed a coherence analysis between local field potentials prior and past of a conditioned stimulus (CS) and investigated the change of the coherence measure over training sessions.

P25: Phytoestrogen modulation of Glutamic Acid Decarboxylase (GAD) Expression and Conditioned Fear Behavior

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Estrogens have been implicated in the development and plasticity of neurons, with profound effects on hippocampus and amygdala–dependent memory and behavior. Evidence suggests, that estrogen receptor-mediated expression of GAD, the key enzyme in γ amino butyric acid (GABA) synthesis, is critically involved in these functions. Here, we investigated the impact of phytoestrogens, estrogen-like plant compounds in animal food, on the expression of GAD and the behavior of GAD mutant mice. High resolution gene expression analysis was performed with laser capture microdissection (LCM) from different subregions of the amygdala, followed by quantitative PCR. Phytoestrogens generally increased the 67kD isoform of GAD (GAD67) levels in the amygdala of wild type mice but effects were limited to the basolateral amygdala in mice heterozygous for GAD67. Also, a significant reduction of NPY expression by phytoestrogen in wild type animals and between-genotype effects on a phytoestrogen-free diet could be observed. These gene expression differences found their reflection in the animals' behavior, as a phytoestrogen diet normalized the auditory cue fear memory deficits observed in GAD67 heterozygous animals. Together, these data suggest that phytoestrogens, via expression regulation of GAD and neuropeptide Y in the amygdala, modulate fear memory formation in mice.

P26: Learning Driven by Reward and Punishment and the Neuromodulation of Acquisition, Retrival and Extinction of two way active avoidance learning by Brain Stimulation and Lesion

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Associative learning can be driven by either appetitive reward or aversive punishments. It is, however, not clear whether the two types of motivation, (approaching appetitive stimuli and avoiding aversive stimuli) drive learning in the same or different ways, nor is their interaction understood in situations where the two types are combined in a single experiment. We investigated the acquisition and extinction of identical behavior reinforced by reward or punishment or both. Specifically, we studied learning of tone-conditioned hurdle crossing in a shuttle box driven by either an appetitive reinforcer (brain stimulation reward) or an aversive reinforcer (electrical footshock), or by a combination of both. Combination of the two reinforcers potentiated speed of acquisition, led to maximum possible performance, and delayed extinction as compared to either reinforcer alone. Additional experiments, using partial reinforcement protocols and experiments in which one of the reinforcers was omitted after the animals had been previously trained with the combination of both reinforcers, indicated that appetitive and aversive reinforcers operated together but acted in different ways: Punishment appeared to be more effective for initial acquisition and reward more effective to maintain a high level of conditioned responses. The results imply that learning mechanisms in problem solving were maximally effective when the initial punishment of mistakes was combined with the subsequent rewarding of correct performance. The Integrative Paradigm was also transferred and adapted to the species mouse (C57 BL/6). The animals were trained in a single response paradigm (shuttle-box) to respond to a change in auditory input (background vs conditioned stimulus) using foot shock as aversive reinforcer or electrical stimulation of the medial forebrain bundle as appetitive reinforcer. The new experimental model permits proteomic analyses of distinct brain regions after appetitive or aversive reinforced learning or a combination of both. Furthermore, in Gerbils using electrical stimulation of either the ventral tegmental area or the lateral habenula can be used to affect the development of tone conditioned avoidance in opposite ways. Previous studies have shown that inactivation of the anterior cingulate cortex (ACC) of rats produced performance deficits in tasks requiring animals to modify their responses according to changes in cue conditions. The present study explores the role of the ACC in the extinction of an active avoidance response by lesioning gerbils after eight conditioning sessions. Extinction training commenced after a week of recovery period, and gerbils were trained for eight sessions. A week after the last extinction session, gerbils were subsequently given retention tests for spontaneous recovery and reinstatement. Results show that lesions of the ACC facilitated extinction learning and attenuated the return of extinguished CRs when gerbils were tested for spontaneous recovery and reinstatement.

P27: Dopamine-modulated spike-timing-dependent-plasticity result in different learning rates for appetitive and aversive reinforcement

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The acquisition of new behaviors through reinforcement learning can be mediated by appetitive or aversive reinforcers or by a combination of both. However, it is still not clear how appetitive or aversive reinforcers act on behavior and how they interact.
Recent findings in Mongolian gerbils demonstrated that changes in behavior can be learned by either appetitive or aversive reinforcers, but the combination of both reinforcers is superior to each single approach (Ilango et al., 2010). Specifically, it was shown that the acquisition of new behavior is fastest when a combination of appetitive and aversive reinforcers is used, slower when only aversive reinforcers are utilized, and slowest for the application of appetitive stimuli. In humans with Parkinson's disease (PD), Frank et al. (2004) where able to show that the effectiveness of appetitive and aversive reinforcement is dependent on the dopamine level. PD patients without treatment typically suffer depleted dopamine levels, whereas the typical treatment with L-Dopa results in increased dopamine levels in comparison to normal controls. Frank and colleagues were able to demonstrate that learning through aversive stimuli was more effective in untreated PD patients, whereas learning through appetitive stimuli was more effective in PD patients with L-Dopa treatment. These results underline that the neuromodulator dopamine plays a key role in reinforcement learning processes. We adapted the spike-timing-dependent-plasticity (STDP) rule to implement reinforcement learning by assuming different STDP kernels for different dopamine levels (Gurney & Redgrave, 2008). At normal dopamine levels (equilibrium), the firing of a presynaptic neuron preceding a postsynaptic neuron results in long-term potentiation of synaptic transmission (e.g., unsupervised learning). If the dopamine level is increased following an appetitive stimulus, the magnitude of the long-term potentiation is increased, whereas for decreased levels of dopamine following a aversive stimulation, the same temporal pattern of pre- and postsynaptic spikes leads to long-term depression.
Using Izhikevich neurons (Izhikevich, 2004) in combination with a biologically plausible winner-take-all (WTA) architecture (Handrich et al., 2009), we implemented a network that exhibits different learning curves for appetitive, aversive and combined appetitive and aversive learning. Networks with WTA architecture can exhibit imperfect learning if the WTA mechanism always favors the same neuron on every trial and inhibits the other, because no STDP mediated plastic changes can occur for a neuron that never fires. To avoid this drawback, we utilized a biologically plausible synaptic scaling mechanism which can prevent silencing of neurons by keeping a neuron's firing rate within a dynamic range (Turrigiano, 2008). The combination of appetitive and aversive reinforcement resulted in the fastest learning, followed by learning through aversive rein.

P28: Age-dependent impairment of fear learning in heterozygous BDNF knockout mice

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´The neurotrophin brain-derived neurotrophic factor (BDNF) has been shown to be important for neuronal survival and synaptic plasticity. Using acute reduction of BDNF signaling in the amygdala, recent studies indicate that BDNF is also crucial for the acquisition and consolidation of amygdala-dependent fear learning. However, in BDNF heterozygous knockout mice which chronically lack BDNF (BDNF+/--mice), no impairment of cued fear learning has been reported so far. In order to analyze this discrepancy between chronic and acute BDNF depletion, we tested fear learning in BDNF+/--mice between 1 and 10 months of age using different fear conditioning procedures, differing e.g. in numbers of tone-shock pairings. We observed a learning deficit in BDNF+/--mice in response to a weak fear conditioning protocol when animals became older than 3 months of age. In control experiments we could show that the observed learning deficit could not be explained by changes in anxiety levels or reduced activity, since these parameters were unchanged compared to wild type littermates. In parallel we measured the electrophysiological properties of these mice and observed an impaired LTP in the thalamic input of BDNF+/--mice (see poster of Meis & Lessmann). ELISA measurements are currently in progress to determine the BDNF-content of the basolateral amygdala of the tested animals in order to delineate a possible correlation between reduced amygdalar BDNF-levels and the reduced learning performance in the aged animals. This is the first study investigating the behavior of BDNF+/--mice over an extended period of time during adulthood. We observed an age-dependent learning deficit in cued fear learning in these mice when they were older than 3 months at the time of testing. We hypothesize that this learning deficit is due to a decrease of amygdalar BDNF-levels, revealing a relevant reduction of fear learning only when BDNF falls below a critical threshold. This study was supported by the SFB779/B6.

P29: Surface mobility of neurexins at active synapses

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The synaptic cell adhesion molecules neurexins (Nrxns) are essential molecules for the function and maintenance of synapses. They are expressed as two major isoforms, alpha- and beta-Nrxn. They share the intracellular domain but differ extracellularly. Nrxns are preferentially targeted to axonal surfaces where they form transsynaptic complexes with postsynaptic molecules like neuroligins or LRRTMs. Using Nrxn-superecliptic-pHluorin (SEP) constructs, we now analysed the surface dynamics of Nrxns in primary hippocampal neurons. Upon overexpression, Nrxn-SEPs showed a widespread distribution over the neuronal surface, and aggregated at synaptic contacts. Exploiting the pH-sensitivity of the Nrxn-SEP constructs, we determined the ratio of intracellular and surface pools of Nrxns in axonal and dendritic compartments, and quantified the fraction of alpha- and beta-Nrxns on synaptic and extrasynaptic cell surfaces. On the axon, more than 90% of alpha- or beta-Nrxn-SEP were at the surface, in contrast to 60-70% on the dendritic membrane. That is consistent with the preferred delivery of Nrxn to the axonal compartment. Next, we analyzed the dynamic behavior of single Nrxn molecules at the surface by using GFP tagged Nrxn constructs, which were labeled with a quantum dots linked to a GFP antibody. The determination between synaptic and extrasynaptic populations was reached by co-labeling active synapses with a fluorescent synaptotagmin or VGat antibody. The surface motility revealed a very dynamic behavior of Nrxns with distinct differences of diffusion properties on axonal extra- and presynaptic membranes. In contrast, dendritic located Nrxns were less mobile and showed a much stronger confinement. Additionally, we found that the dynamics of axonal Nrxns differs between inhibitory and excitatory neurons. Nrxns are stronger confined in inhibitory synapses compaired to excitatory. Removal of extracellular Ca2+ as well as deletion of the extracellular domain of Nrxns increased the diffusion coefficient, suggesting attachment to postsynaptic binding partners as a putative determinant. In contrast, co-expression of alpha-Nrxn together with the ligand Neurexophilin drastic reduced alpha-Nrxn mobility. Together, these results suggest a very dynamic behavior of important presynaptic adhesion molecules, which are suggested to play a dominate role in the maintenance of synapses.

P30: Molecular mechanisms of dopaminergic memory modulation

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In Mongolian gerbils, the auditory cortex is critical for the discrimination of rising versus falling frequency-modulated tones (FMs). In this paradigm, long-term memory formation is enhanced by local infusion of the D1/D5 dopamine receptor agonist SKF-38393 into the auditory cortex shortly after or even one day before the learning event. This effect is sensitive to rapamycin and anisomycin, suggesting that dopaminergic activity in the auditory cortex may induce mTOR-dependent translational changes that support memory consolidation for hours or days. To identify proteins differentially expressed one day after the injection of SKF-38393 into the auditory cortex of naïve gerbils, proteomic analyses were performed. Two-dimensional gel electrophoresis of subcellular fractions revealed changes in the protein profiles of the auditory cortex itself, and of distant cortical and subcortical brain structures known to receive direct or indirect projections from the auditory cortex. These include the hippocampus, frontal cortex, and striatum, i.e., brain structures implicated in long-term memory formation through novelty computation, salience attribution, and reward processing. At the molecular level, dopamine agonist-induced changes involved, in part, proteins with putative functions in the regulation of synaptic signaling (e.g., alpha-synuclein, 14-3-3) and of local protein synthesis (e.g., RNA-binding proteins). The functional relevance of alpha-synuclein – a primarily presynaptic, mTOR-regulated protein – for FM discrimination learning was analyzed further using mice of an alpha-synuclein deficient C57BL6 substrain. These mice were able to learn the discrimination task but with different kinetics when compared to mice of two alpha-synuclein expressing C57BL6 substrains. Specifically, during the initial days of training, alpha-synuclein deficient mice learned the FM discrimination faster than non-deficient mice. Later on, however, at the asymptotic part of the learning curve, non-deficient mice reached a higher final level of discrimination performance than alpha-synuclein deficient mice. Augmentation and attenuation of these differences by dopamine agonist and antagonist treatment, respectively, suggest an involvement of alpha-synuclein in dopaminergic mechanisms of memory modulation. Together, our findings suggest that dopaminergic neurotransmission in the auditory cortex may induce changes in the expression, modification and/or distribution of specific brain proteins, such as alpha-synuclein, which are involved in the modulation of long-term memory required for the discrimination of complex sounds. Supported by the DFG (SFB 779).

P31: Activity-dependent synaptic plasticity evokes Jacob translocation to the nucleus in hippocampal neurons after stimuli inducing long-term potentiation but not long-term depression

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In neurons multiple signalling pathways converge in the nucleus to regulate the expression of genes associated with long-term structural changes of synaptic inputs. Synapse-to-nucleus communication is particularly important for this type of transcriptional regulation. One of the ways for synapse to nucleus communication is activity dependent translocation of protein messengers. In recent years a number of synapto-nuclear protein messengers have been characterized that exhibit activity-dependent nucleocytoplasmic shuttling and that are thought to be involved in plasticity-related gene expression. However, there is a paucity of data showing the nuclear import of such proteins in cellular models of learning and memory. In previous work it was shown that the nucleocytoplasmic shuttling of Jacob is involved in NMDA-receptor signalling to the nucleus and CREB mediated gene expression in hippocampal primary neurons. Jacob transcripts and protein are readily detected in cortex and limbic system. Extended cellular and subcellular expression studies in rat hippocampal slices demonstrated that Jacob is expressed only in pyramidal cells of CA3-CA1 regions, granular cells in DG and all types of interneurons but not in glia. Since Jacob is localizesd in the cells types involved in neuronal plasticity we aimed to study whether Jacob accumulates in the nucleus in physiological relevant model systems. To this end, we have analyzed the dynamics of Jacob nuclear import following induction of NMDA-receptor dependent early and late forms of long-term potentiation (LTP) or long-term depression (LTD) at CA1 synapses in acute hippocampal slices . Interestingly, only strong stimulation protocol inducing late-LTP was increasing significantly Jacob immunofluorescence in the nucleus. Using molecular imaging of virus-transfected slices with a Jacob-GFP construct we indeed found that Jacob rapidly translocates already during the tetanization period of LTP and but not LTD to the nucleus. Complementary findings were obtained after induction of chemical LTP and LTD in hippocampal primary neurons suggesting that Jacob translocates into the nucleus only after NMDAR-dependent LTP. Thus Jacob represents a protein that could be involved in mechanisms of memory consolidation.

P32: Dopaminergic Modulation of Learning-Dependent Plasticity in human auditory cortex?

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There is experimental evidence that cholinergic inputs from the basal forebrain modulate learning-dependent plasticity in the human auditory cortex (AC). However, animal data indicate that the dopaminergic and noradrenergic system might also contribute to this process. In order to investigate the dopaminergic influence, we performed a complementary fMRI/MEG study using an appetitive operant conditioning paradigm. In the course of the experiment, subjects had to learn to associate a specific class of frequency-modulated sweeps (FMs) with a monetary reward for fast reactions in a consecutive reaction-time task. If learning-dependent plasticity occurs within the AC, neural responses to the reward-predicting stimulus should be modified after the stimulus-reward association had been learned. Moreover, if dopamine promotes this effect, functional plasticity should coincide with an increase of neural activity in dopaminergic midbrain areas for reward-predicting FMs.
18 subjects took part in the fMRI study, 34 in the MEG study. At the beginning of each trial, a FM indicated whether the upcoming trial was potentially rewarded or not. Subjects had to learn by trial and error, which sound feature—loudness, pitch interval, pitch alternation rate, pitch direction, or stimulus duration—predicted a potential reward; stimulus duration served as the reward-predicting dimension (CS+/CS-). In the fMRI study, we found significant effects in the interaction between stimulus type (CS+/CS-) and learning status in the ventral tegmental area (VTA), but not in the AC. The neural activation level in reaction to CS+ was also contrasted with CS- in a time interval confined to the period after the completion of the learning phase. Here, we found additional activation foci along the auditory pathway in the inferior colliculi (IC) and the medial geniculate nuclei (MGN). Similar effects were observed bilaterally in both the insular cortex and the caudate nucleus, but again not in the AC. Our findings are in line with studies in animals in which duration-selective neurons were identified within the IC, thus providing evidence for functional plasticity in both the IC and the MGN. With respect to the time course of neural activity in the VTA, our data point towards a role of dopamine in learning-dependent auditory plasticity in humans. In contrast to the fMRI findings, in which no significant effects in the AC were found, our preliminary MEG results indicate the occurrence of a task-related effect in the AC. The peak latency of the M100, the most prominent auditory evoked magnetic field, was larger in the left compared to the right hemisphere, dependent on whether the subjects were able to solve the learning task or not. There are also indications that the energy of the sustained field and the peak-latency of the stimulus-offset are related to the subject's performance in the learning task. The work was supported by the SFB TR 62 of the DFG.

P33: A dopamine agonist compensates for the LTP impairment resulting from amyloid ß oligomers

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Alzheimer's disease is the most common form of dementia among elderly population. Recent studies implicate small soluble aggregation forms of amyloid ß, so called Aß oligomers, as potent mediators of neuronal dysfunction. In particular, oligomeric Aß is described to impair long-term potentiation (LTP) of synaptic response. As LTP is an excepted cellular correlative of learning and memory, its disruption by Aß oligomers may be causative for early memory deficits and cognitive decline in Alzheimer patients. In previous studies, we and others found that application of Aß oligomers to hippocampal slices impairs long-term potentiation LTP in the apical dendritic layer of CA1 and decreases in neuronal network activity (Rönicke et al., 2010). Dopamine is directly involved in the synthesis of plasticity-related protein, via cyclic adenosine monophosphate (cAMP) and protein kinase A (PKA) and it has been demonstrated to be involved in the induction of late-LTP in the CA1 region of the hippocampus (Frey et al., 1991) and can convert a weak-LTP into a late-LTP.
We therefore investigated whether a dopaminergic, particularly a D1/D5 receptor stimulation, would be able to compensate for the detrimental Aß effect on LTP magnitude. 0,5-5 µM of SKF 38393, an agonist of D1/D5 receptors, was applied after the slice Aß preincubation period and before and during the LTP induction. Field-EPSP were recorded from mice stratum radiatum before and after a conventional strong tetanization of the Schaffer collaterals. ndeed SKF 38393, rescued the Aß-impaired LTP. Interestingly, this effect appeared already at early LTP stages. Under our experimental conditions an application of SKF 38393 alone did not enhance LTP, suggesting that activation of D1/D5 receptors and application of oligomeric Aß induce downstream signals which are linked. Further studies are now planned to reveal the underlying mechanism of reversing Aß-mediated LTP disruption with SKF 38393. Rönicke R, Mikhaylova M, Rönicke S, Meinhardt J, Schröder UH, Fändrich M, Reiser G, Kreutz MR, Reymann KG. Neurobiol Aging. 2010, Epub ahead Frey U, Matthies H, Reymann KG, Matthies H.: Neurosci Lett. 1991, 29:111-4.

P34: Auditory working memory: Physiological mechanisms in human and monkey auditory cortex

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Evidence has accumulated that the auditory cortex (AC), and not only prefrontal cortex, is directly involved in auditory working memory, but the underlying physiological mechanisms of working memory in AC are poorly understood. This project aims at identifying physiological correlates of auditory working memory in the AC, using a convergent approach in which neuronal activity in the AC was monitored by means of whole-head agnetoencephalography (MEG) in humans and micro-electrode recordings of action potentials and local field potentials in monkeys. In the MEG study, 12 subjects listened to pairs of brief tones (100 ms duration, stimulus onset interval (SOI) 2 s), presented to the left ear. A-tones had a frequency of 1.5 kHz and B-tones of 1.6 kHz. In one condition, subjects had to press a response button when two A-tones occurred in succession, thus had to memorize the first A-tone, but not the B-tone. In the second condition, the target was a pair of B-tones, so that subjects had to memorize the initial B-tone, but not the A-tone. We analyzed brain responses during the silent intervals between the tones and compared memorized with non-memorized conditions. We employed a source model consisting of 11 regional sources (RS) distributed over the whole brain. Two RS, one in each hemisphere, were seeded at the border of Heschl's gyrus and the planum temporale, based on the MR image of the individual subject's brain. The vector sum of the two components of each RS allowed a reliable calculation of activation at every sample point (sampling interval 1.475 ms) separately. In each hemisphere, the auditory RS showed a clear increase in activation in the memorized condition, in comparison with the non-memorized condition. This result suggests that an auditory memory load may be accompanied by sustained activity of neural sources in the AC. First results of the spectral analysis of the source waveforms during the final 1.5 s of the silent interval between the tones of a pair indicate a decrease of power in the alpha band in the memorized condition, in both AC. In the non-human primate part of this study, using instrumental conditioning, we trained two macaque monkeys to perform the same working memory task with similar tone pairs presented at an SOI of 0.8 s. After extensive training, action potentials and slow wave field potentials were recorded simultaneously from the right AC of one monkey during task performance. Similar to what we found in humans, analysis of action potentials for correctly responded trials showed sustained activity during the inter-tone interval in the memorized condition, but not in the non-memorized condition, despite identical tone pairs. Our results both in human subjects and non-human primates suggest that AC is involved in working memory. Potential correlates of working memory—sustained firing and brain oscillations—could be identified within the AC. The work was supported by an IfN Special Project Grant to RK, PH, and MB.

P35: Role of different neuromodulators for the induction and maintenance of L-LTP in hippocampal basal CA1-dendrites

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Long-term potentiation (LTP) is considered as a cellular model suitable for studying synaptic changes that likely occur during learning and memory formation. LTP has distinct phases, thus a transient protein synthesis-independent stage (E-LTP) can be followed by a late, long-lasting and protein synthesis-dependent stage (L-LTP). In hippocampal neurons, L-LTP requires the heterosynaptic associative activation of glutamatergic as well as neuromodulatory inputs during its induction, which can be provided by afferents from different cortical and subcortical brain structures. For LTP induced in apical dendrites of the CA1 region we had shown earlier, that the synergistic activation of glutamatergic NMDA-receptors together with dopaminergic receptors is required (Frey et al, 1990, 1991, 1993, 1998). We had shown later on that glutamatergic function is mainly involved in the induction and maintenance of E-LTP as well as in setting of a transient synaptic tag (Frey and Morris, 1998) whereas the neuromodulatory input activates, in a synergistic interaction with NMDA-receptor function, the synthesis of plasticity-related proteins (PRPs) which can bind to synaptic tags and thus transforming E-LTP into L-LTP and thus guaranteeing the prolonged maintenance of LTP (for review see Frey and Frey, 2008). LTP, however, in either the apical (stratum radiatum) or basal CA1-dendrites (stratum oriens) differ in their innervation, molecular requirements during their induction, the nature of tag molecules as well as required PRPs (Sajikumar et al. 2007). These data resulted in a theory of functional compartments differentially processing local information (Frey and Frey, 2008). Here we investigated whether LTP in the stratum oriens requires similar or other synergistic interactions with respect to the neuromodulatory systems involved when compared with the stratum radiatum. We show the effects of dopaminergic, adrenergic, serotonergic, cholinergic as well as metabotropic glutamatergic receptor blockers as well as the role of voltage-dependent calcium channels in the regulation of LTP induced in the basal CA1-dendritic branches. Our results support our earlier data, that L-LTP in basal dendrites requires different mechanisms for its induction and maintenance when compared with L-LTP in apical CA1-dendrites.

References: Frey et al. (1990) Brain Res. 522; Frey et al. (1991) Neurosci. Lett. 129; Frey et al. (1993) Science 260; Frey and Morris (1998) TINS 21; Sajikumar et al. (2007) J Neurosci 27; Frey and Frey (2008) Prog Brain Res 169. Acknowledgement: We are grateful to Diana Koch and Anja Apel for their technical assistance. This work was supported by project fund from DFG FR-1034, SFB 779 B4 to JUF and a Humboldt fellowship to SP.

P36: A dynamic framework for cortical processing during learning

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To become behaviorally relevant, sensory information is generally embedded in a broader cognitive context through learning. On a cognitive level, this leads for example to the formation of categories. On a neural level, this would require a further interpretaion of sensory information by read-out mechanisms. Here, we want to present two directions of combined electrophysiological and behavioural research to investigate the cortical processing steps related to the meaningful interpretation of sensory information during perceptual learning and category formation in Mongolian gerbils.
In studies on category learning, we examined whether perceptual categories formed in the auditory modality can be transferred to the visual modality by the abstraction of shared features from the specific sensory experiences. We observed that spatiotemporal activity patterns of the ongoing EEG of the auditory and visual cortex were associated with both, auditory and visual stimuli, exclusively in animals successfully performing transfer learning. To investigate dynamic neuronal interactions of both sensory categories under the focus of associative memory we analysed phase coherence between oscillatory components of local field potential activity (LFP, 7-200 Hz) measured in auditory and visual cortex. Our results suggest that a repeated association of audiovisual stimulus pairs (Flash/Tone or Tone/flash) after a sufficient number of trials leads to a second perceptual event, even when the second stimulus is omitted. In further studies we used artificial intracortical microstimulation (ICMS), in order to provide causal links between cognitive and neural processes during learning. By targeting different cortical input and output layers of auditory cortex, we activated separate subsystems of the cortical microcircuitry as revealed by current-source-density (CSD) analysis. We studied local and wide-spread cortical processing during ICMS and its interference with ‘natural’ auditory evoked responses in combined electrophysiological and behavioural experiments. We could demonstrate that behaviorally detectable cortical activity originates from driving excitatory recurrent corticothalamic feedback loops, which provide stable, reentrant information that can be read out by global horizontal cortical processing systems. Using ICMS we could also show that this read-out is a non-local phenomenon, which reveals the important role of wide-spread global cortical spatiotemporal activation patterns in cognitive interpretation of sensory information.

P37: The effects of digestion of extracellular matrix on the network activity in neuronal cultures

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Extracellular matrix (ECM) is a structure on neuronal surface that surrounds synapses and consists of glycoproteins and proteoglycans. Its development coincides with maturation of synapses and provides a basis for structural stability of established synaptic contacts. The analysis of ECM distribution among different neuronal classes shows that it is present predominantly on GABAergic interneurons. It has been shown earlier that ECM restricts the lateral mobility of membrane receptors, thus affecting the amount of those available for synaptic transmission. In vivo, development of ECM has been reported to have an inhibitory effect on experience-dependent plasticity, and degradation of ECM restored cortical plasticity to juvenile levels. Taken together, these findings suggest that ECM is involved in modulation of synaptic plasticity and memory processes. In present study, we analysed the effect of digestion of ECM by Hyaluronidase (HYAL) on network activity in matured neuronal cultures. Rat hippocampal cultures (E18, density 500K-1M) were plated on 60-channel microelectrode arrays and incubated at 37°C for at least 28DIV. Further, we recorded their spontaneous extracellular activity prior to and after treatment with HYAL. Neuronal cultures treated with inactive HYAL served as controls. We found that ECM digestion leads to marked changes in several parameters of neuronal activity, including mean duration of bursts, amount of spikes per burst, and mean firing rate within bursts. Additionally, a significant increase of the amplitude of oscillations in theta and gamma frequency ranges was evident for periods during bursting, but not for inter-burst intervals. Our data demonstrate that the digestion of ECM significantly affects neuronal activity on the population level, which can be mediated by modulation of contribution of interneurons into network activity. Our results suggest that the removal of ECM in mature neuronal population alters properties of neuronal interaction and can play a permissive role for short-term plasticity.

P38: Single-cell resolution mapping of neuronal activity in cerebral cortex using the K+-probe thallium as a tracer

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In neurons K+-permeability, Na,K-ATPase activity and, hence, the rate of K+-uptake increase with increasing activity. K+-analogues, like the heavy metal ion thallium (Tl+), can be used, therefore, as tracers for imaging neuronal activity. Animals can be systemically injected with thallium (Tl+) salts, and the Tl+-uptake patterns in the brain can be mapped at the light and electron microscopical level using a histochemical method for the detection of heavy metals, a modified Timm-technique or autometallographic method. However, when water-soluble Tl+-salts are injected systemically only minute amounts of the tracer enter the brain and the Tl+-uptake patterns are influenced by regional differences in blood-brain barrier (BBB) K+-permeability. We have recently shown that the BBB-related limitations in using Tl+ for imaging neuronal activity are no longer present when animals are injected with the lipophilic Tl+ chelate complex thallium diethyldithiocarbamate (TlDDC) (Goldschmidt et al. 2010, Neuroimage 49:303-315). We have developed a protocol for mapping neuronal activity with cellular resolution, which is based on intravenous TlDDC injections during ongoing activity in unrestrained behaving animals and short stimulation times of five minutes.
We here used this novel technique for mapping neuronal activity in cerebral cortex of Mongolian gerbils under a variety of different conditions. Upon intracortical microstimulation Tl+-uptake increases markedly in neurons at the stimulation site. Upon pharmacological inhibition with muscimol neuronal Tl+-uptake decreases markedly. Upon stimulation with pure tones tonotopically organized bands of increased neuronal Tl+-uptake can be found in the auditory cortex. No such bands are present when animals are stimulated with amplitude modulated broadband noise.Tl+-uptake patterns at the cellular level are highly complex. In awake behaving animals Tl+-uptake is high in layer V pyramidal neurons and in large non-pyramidal cells in layer IV most likely representing fast firing interneurons. Tl+-uptake patterns in putative interneurons vary with stimulation conditions and differ between animals stimulated with pure tones or amplitude modulated broadband noise.

P39: shRNA mediated knockdown of proteins relevant for activity dependent secretion in neurons

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The mammalian neurotrophins are important regulators of a variety of functions that are necessary for neuronal development and neuronal plasticity. Like other neuropeptides, neurotrophins are stored in secretory granules and are released upon specific electrical stimulation. In comparison to the knowledge of the molecular machinery meditating synaptic vesicle exocytosis underlying neurotransmitter release, the mechanisms of secretory granule exocytosis in neurons are less well understood. To investigate the molecular mechanism of activity-dependent release of neuropeptides, we have designed a new generation of shRNA expression vectors enabling functional knockdown analysis. In order to analyse the machinery of secretory granule exocytosis by live cell imaging, dissociated hippocampal neurons derived from mouse were genetically manipulated by simultaneously knockdown of secretory relevant proteins and knock-in of a GFP labelled neurotrophin (BDNF-EGFP). To perform these simultaneous genetic manipulations, we established a protein knockdown using of a new generation of shRNA expressing plasmids. These vectors are based on the transcription of the shRNA of interest which is further matured to the requested siRNA by the endogenous miRNA processing machinery. To quantify the functionality of the plasmid and the degree of knockdown, cultured hippocampal neurons were cotransfected with a plasmid expressing GFP and the siRNA coding plasmid against GFP. The knockdown efficiency was analysed by measuring the intracellular fluorescence intensity of GFP in knockdown cell compared to control cells. An efficient knockdown of GFP of more than 83% was observed 3 days after transfection. To establish a similar efficient knockdown of proteins relevant for secretion, the knockdown plasmid was modified to express an shRNA directed against CAPS1, a protein known to mediate dense core vesicle exocytosis in neuroendocrine cells. The knockdown efficiency of this plasmid was analysed in a same fashion revealing a knockdown of more than 47 % within 3 days after transfection and more than 75% within 7 days after transfection. Hippocampal neurons transfected with the CAPS1 knockdown plasmid were stained with an antibody directed against CAPS1 demonstrating the knockdown of endogenous CAPS1 protein. Taken together we have established an efficient method for simultaneous knockdown of different proteins to analyse the machinery of secretory granule exocytosis. This project is part of the graduate program GRK 1167 supported by the Deutsche Forschungsgemeinschaft (DFG)

P40: Electrical properties of CA1 pyramidal neurons after RNA interference-mediated knockdown of BDNF in single CA1 pyramidal neurons

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The protein BDNF is a member of the mammalian neurotrophin family. Beside the important role of BDNF in neuronal survival and differentiation, BDNF is a critical regulator of acute and long-term changes in synaptic plasticity. At the synaptic level, BDNF has both, pre- and postsynaptic effects. The application of BDNF acutely stimulates neurotransmitter release and phosphorylation of ionotropic receptors, which can drive fast changes of glutamatergic and GABAergic synaptic transmission. Long term application of BDNF to neuronal cultures regulates morphological synaptic changes, enhances glutamatergic as well as GABAergic transmission by pre- and postsynaptic mechanisms and is also a mediator of synaptic homeostasis. Moreover, studies with BDNF knockout mice confirm the significance of BDNF in acute and long-term regulation of synaptic transmission. Many of these studies have been performed by unrestricted administration or withdrawal of BDNF in complex networks. But the impact of BDNF expression level in a single neuron on the basal synaptic transmission is unknown. To aquire a refined understanding of the more subtle synaptic changes caused by BDNF, knockdown of the neurotrophin at the single cell level is needed.
To investigate the consequences of an individual BDNF-deficit we developed an efficient method to down-regulate the BDNF protein level in a single CA1 pyramidal cell. Therefore, organotypic hippocampal slices were prepared according to the Stoppini method. Selected CA1 pyramidal neurons were then cotransfected by single-cell electroporation with pEGFP N1 and a validated siRNA at 8 DIV. So, with an siRNA directed against GFP we could reduce the EGFP protein level to below 10%. Then, cells, electroporated with pEGFP N1 and a validated siRNA targeting BDNF or a non-silencing control siRNA were characterized electrophysiologically using the whole cell patch clamp technique three days after transfection. The comparison of basal electrophysiological properties revealed no significant differences between control and BDNF-deficient cells in a BDNF containing cellular context. With respect to our results we suggest that the BDNF containing environment compensates for a BDNF-deficit in a single CA1 neuron. (supported by SFB 779 and the Schram Stiftung)

P41: Haplodeficiency for GAD65 provides resilience in a mouse model of posttraumatic stress disorder

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Neurobiological processes related to posttraumatic stress disorder (PTSD) can be modelled in rodents, using a paradigm of combined juvenile stress and adult trauma. Here, we investigated the response of mice with haplodeficiency in the gene for glutamic acid decarboxylase 65 (GAD65+/- mice) in this paradigm in order to analyse the potential role of GAD65-mediated GABA synthesis in the development of PTSD-related disturbances. GAD65+/- mice are known for a delayed maturation of the GABAergic system, but show normal emotional behaviour in the adulthood. In the current experiments, GAD65+/- mice and their wild type littermates were analysed in a battery of emotionality tests, immediately before and 2 weeks after auditory fear conditioning serving as the adult stressor. Our data show that heterozygosity for GAD65 prevents animals from developing an exaggerated fear response to the background context as was observed in wild type animals. No comparable effect was observed in mice haplodeficient for the second GAD-isoform, GAD67. Moreover, auditory cued fear memory, as well as different measures of anxiety-like and depression-related behaviors were unaltered between GAD65 genotypes. Age controls confirmed the specificity of these effects and the normal conditioned fear response of adult GAD65+/- mice. Together, these data indicate a specific role of GAD65-mediated GABA synthesis in the development of posttraumatic stress symptoms. Supported by grants of the German Research Foundation (Deutsch-Israelische Projektkoordination) and the Fritz Thyssen Stiftung.

P42: Neuronal activation in the primate auditory cortex during learning of bi-modal audio-visual task performance

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Recent data on learning-related changes in animal and human auditory cortex indicate functions beyond mere stimulus representation and simple recognition memory for stimuli. The final result of similar researches, in an ideal, is an investigation of the given functions in human. But some experimental procedures cannot be applied to human, thus as the closest and adequate object of research we used long tailed macaque (Macaca fascicularis).
We studied neuronal activity in the auditory cortex, along with an assessment of behavioral performance during intensive learning and sensory-motor task fulfillment.
The macaque was trained to perform a bi-modal audio-visual task after the presentation of an audio or visual instruction, followed by the simultaneous presentation of both auditory and visual stimulation. Stimuli congruent with the instruction are regarded as targeting whilst conflicting stimuli are regarded as distracting. In order to obtain a reward (water), the monkey must correctly perform a task by first grasping a bar when the stimulation is presented, then by releasing the bar once the target stimulation is presented in its complete form.
Behavioral data shows that in the case of foremost ending of targeting stimulation, the reaction time was significantly shorter and performance was significantly higher than in the case when distraction preceded stimulation. We found many acoustically responsive sites in the primary auditory cortex, where firing was synchronized to either the presentation of the instruction, the onset and offset of the stimulation, or when grasping and releasing the bar. Of 162 multiunit firings, 105 were related to auditory instruction, 3 were related to visual instruction, 94 were related to auditory-visual stimulations onset, 130 were related to auditory stimulation offset, 81 were related to visual stimulation offset, 74 were related to grasping the bar and 116 were related to releasing the bar. Presentation of the visual instruction induced neuronal activity from several sites in the auditory cortex. Peak activity occurred during auditory stimulation offset; this activity was reduced by 15% during visual stimulation offset and by 40% during auditory-visual stimulation onset. We also observed a relationship between the size of the reward, and the number of active sites relating to auditory stimulation offset. Neuronal firing was at its peak during whole hand movements, such as grasping and especially releasing the bar. It was found that the number of active neuronal sites related to releasing the bar exceeded the number of sites related to grasping the bar by a factor of 1.5.
These data indicate the existence of cross-modal activation in the auditory cortex in response to both hand movement and visual stimuli. We therefore suggest that this multimodal representation in the auditory cortex in primates emerged owing to intensive learning and practice in performing bi-modal tasks.

P43: Role of proteolysis in extracellular matrix remodeling

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During late neuronal development after the establishment of neuronal networks, a condensed, brain-specific extracellar matrix (ECM) peculiarity, the so-called perineuronal nets, is formed. It consists of proteoglycans and glycoproteins of both neuronal as well as glial origin. This specialized structure has been found to function in synapse stabilization and affects long- as well as short-term plasticity. It is known for a long time that many of the components of the ECM are proteolytically processed, mainly by the large protein family of matrix metalloproteases (MMPs). Little is known about the significance or the regulation of this process. Therefore, we used western blotting to investigate the processing of one of the most prominent components of the mature ECM, brevican, during different modes of synaptic activity. Furthermore, we cloned a number of metalloproteases such as MMP 3, MMP 13 and ADAMTS4 in order to study their potential to process brevican and their subcellular localization.

P44: Jacob decodes in the nucleus the synaptic or extrasynaptic origin of NR2B-NMDA receptor signals

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In hippocampal excitatory neurons NR2B-containing subunits of the NMDA-receptor are located at synaptic and extrasynaptic sites. There is an apparent functional discrepancy between synaptic and extrasynaptic NMDA receptors: their activation leads to fundamentally different consequences in terms of nuclear gene expression. The underlying mechanisms for this sharp distinction are till now essentially unclear. Previous work has shown that the Jacob's nuclear translocation is instrumental for NMDA-receptor mediated gene expression and the CREB shut off pathway. In this study we show that Jacob is exclusively part of the NR2B but not of the NR2A receptor complex. Most importantly after stimulation of synaptic but not of extrasynaptic NMDA-receptors its nuclear translocation requires ERK activity. Jacob is an ERK binding protein and is phosphorylated by ERK at a Ser180. Importantly, Jacob is phosphorylated at this position only after activation of synaptic NMDA-receptors. Nuclear overexpression of a Jacob mutant that can't be phosphorylated at Ser180 causes destabilization of synapses, simplification of dendrites and gene expression in favour of reduced plasticity and cell survival. The opposite is found with a phospho-mimicking mutant at this crucial position. Of note, this is independent of synaptic activity. Thus, even after blockage of synaptic neurotransmission the cells overexpressing the phospho-mimicking mutant in the nucleus react with a gene expression pattern and subsequent morphological changes that are characteristic for enhanced synaptic strength. In other terms the presence of ERK-phosphorylated Jacob suggests the nucleus that plastic events must have happened at the cells synapses despite these synapses were silent. Hence, the presence of non-phosphorylated Jacob suggests the opposite and is followed by a series of deteriorative events in terms of synaptic integrity that subsequently leads within a few days to neuronal cell death.

P45: Alteration of reward in an animal model of depression – the olfactory bulbectomy

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Affective disorders and substance abuse frequently coexist in patients. Thus, comorbidity of substance abuse and mentally ill is an important problem for modern psychiatry.
We intended to investigate relations between depression and reward mechanisms using a validated animal model. The bilateral olfactory bulbectomy in rats is considered to be a relevant animal models of depression. The olfactory system in the rat represents an important part of the limbic system in which the hippocampus and the amygdale contribute to emotional and memory components of behaviour. Olfactory bulbectomy results in a retrograde degeneration of the neurons that project to and from the main and accessory olfactory bulbs. Neuronal degeneration also occurs in the hippocampus and amygdala after olfactory lesion. Bulbectomized rats exhibit stable impairments of neurochemical and neuroendocine mechanisms which are associated with measurable behavioural changes and which show striking similarities to disturbances observed in peoples with major depression. Behavioural disturbances in bulbectomized rats are normalized following chronic antidepressant drug administration. We used the bulbectomy model for investigation of reward mechanisms in to different experimental paradigms, the self-administration of ethanol and the conditioned place preference to ethanol. We found the voluntary ethanol intake increased in bulbectomized rats in a drinking experiment. Conditioned place preference was induced in control rats using 0.25mg/kg body weight ethanol, whereas bulbectomized animals needed a higher dose. The dose dependent sedative effect of ethanol was also decrease in bulbectomized rats compared to sham operated rats. However, the hypothermic effect of ethanol was similar in both experimental groups. Taken together, the results suggest, that the mechanisms of reward are altered in this animal model for depression. The rewarding effects of ethanol seem diminished in bulbectomized rats. The findings reveal the utility of the bulbectomy model in rats for studying the neurobiological basis of depression and the comorbidity of depression and drug abuse. Moreover, they support the hypothesis that the addictive, respectively the rewarding properties of some drugs of abuse are modified in depression. The results also demonstrate that effects of a substance may be specifically changed in bulbectomized rats, depending on the brain region mediating these effects.

P46: Biological Basis for Individual Differences in Social Decision Making – Evidence in Genetics and fMRI

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Investigating human social behaviour under adequate experimental conditions has remained a challenge. Neuroeconomics though provide very useful paradigms – that is their different kinds of economic games. Early economic models of human decision-making have almost entirely ignored the influence of emotions on people's decision-making behaviour. In recent years, behavioural economists have identified psychological and emotional factors, which influence decision-making. Recently, methods of neuroimaging have been used to describe the neurobiological basis of economic decision-making as kind of social behaviour. Above all first papers have already shown that social decision-making in economic games can be linked to specific genes. In a further step we aimed to investigate the biological basis of individual differences in economic decision-making, using the 'Social Value Orientation Task' (SVOT). In our first study, a total of 258 young healthy subjects took part in an online version of the SVOT. Besides playing 24 games of the SVOT all subjects were genotyped for AKAP5 Pro100Leu, a rare investigated polymorphism in the AKAP5 gene. The human AKAP5 gene product (AKAP79) is expressed in several CNS regions that have been linked to emotional and motivational processes, including the amygdala, the hippocampus and the striatum. Preliminary studies carried out in our lab indicate that the AKAP5 Pro100Leu polymorphism is associated with human anger and aggression. In particular, carriers of the less common Leu allele (15.6% allele frequency) score significantly lower in physical aggression and higher in anger control. We therefore aimed to proof, if the AKAP5 Pro100Leu polymorphism might also affect impulsivity and emotionality within the SVOT. Subjects' decisions within the test were incentivized with monetary payoffs, reaching average earnings of about 9.87 Euro. Based on their decision-behavior, our subjects could either be classified as 'prosocial' (a total of 116 subjects) or as 'proself' (a total of 129 subjects). We found that Leucine-carriers are less likely classified as 'pro-social' than proline-homozygotes (Fisher's exact test, two-sided, p=0.009). The choices of subjects carrying leucine are less cooperative and thus lead to a smaller resulting angle in the so-called ring-measure (Mann-Whitney-U test, two sided, p = 0.010). In an additional fMRI-study we were interested in brain responses elicited by the same decisions made by participants differing in their habitual response tendencies.
Participants played a series of different binary dictator games whilst in the scanner. From their decisions we identified three types of participants, with different patterns of behavior. Significant differences in brain activity of the three types were observed even in trials in which they made identical decisions suggesting a different balance of emotional and cognitive processes bearing on their decision.

P47: Oscillations in the human thalamus dissociate novel and familiar stimuli

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Introduction
Converging evidence shows that the hippocampus plays a central role in novelty processing. Especially hippocampal theta and alpha oscillations seem to be a main ingredient of signalling novel events. As a part of the Hippocampus-VTA loop and a transmitter between Globus Pallidus internus and Cortex, the Thalamus is hypothesized to display oscillatory behaviour as well.
Methods
Five patients (65-74 years) were implanted a depth electrode in the VIM nucleus of the thalamus to be treated with Deep Brain Stimulation (DBS) for therapy-refractory typical essential tremor (3 cases), atypical essential tremor (1 case), or tremor-dominant Parkinson's disease (1 case). Before the implantation of the pacemaker we were able to record local field potentials and scalp EEG simultaneously.
Patients performed a simple visual odball task. Complex outdoor scenes from four different categories were shown randomly. Baseline and target pictures were frequent events, whereas unknown as well as pre-familiarized known items were presented rarely.
To achieve information about the time-frequency characteristics of the electrophysiological data, we analysed the data by means of a Continuous Wavelet Transform.
Results
We were able to dissociate the electrophysiological responses to novelty and familiarity in the thalamus. The most pronounced difference was an increase in high theta/low alpha for novel stimuli at about 200ms after stimulus onset and a later increase in low theta for known stimuli. A similar response could be observed on the scalp at about 400-600ms. Analysis of the three contacts in the thalamus suggest that the signal could be composed of a more ventral alpha response and a dorsal theta response.

P48: Motivational salience specifically modulates repetition suppression in the anterior hippocampus

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Introduction:
Repetition suppression is a rapid decrease of stimulus-specific neuronal responses upon repeated presentation of a stimulus. Previous studies have demonstrated that negative emotional salience of stimuli enhances RS in stimulus-related brain regions. It is, however, unclear how positive motivational salience, such as reward prediction influences repetition suppression for complex visual stimuli, and which brain regions might show differential RS for reward-predicting and neutral stimuli.
Methods:
Here we investigated the influence of motivational salience on RS of complex scenes using event-related fMRI. 30 young healthy volunteers (24,6 ±2,27 years, 16 females) performed a monetary incentive delay (MID) task. Complex scenes (indoor vs. outdoor) served as cue pictures, with one category indicating an upcoming reward or neutral outcome in a reaction time task. Each cue picture was repeated three times. Statistical analysis was performed using SPM8b and a standard mixed effects model, and fMRI responses to cues were statistically compared as a function of reward association and repetition.
Results:
In line with previous findings, reward anticipation (i. e. reward cues vs. neutral cues) was associated with activations in the ventral striatum, orbitofrontal cortex, midbrain, and subthalamic nuclues. Stimulus repetition was associated with a continuous response decrease (i.e. repetition suppression) from the 1st to the 3rd presentation. While repetition suppression could be reliably observed across visual area association cortices, prefrontal and parietal brain regions, it was largely insensitive to reward association of the stimuli. An interaction of reward anticipation and repetition suppression was specifically observed in the anterior hippocampus, where a response decrease from the 1st to the 3rd presentation was observed for the reward cues only.
Conclusions:
The results of the present study suggest that hippocampal – unlike neocortical – repetition suppression is sensitive to motivational salience of stimuli. Further research should be directed at a potential role of hippocampal RS in the previously observed preferential long-term encoding of rewarded stimuli into hippocampus-dependent memory.

P49: External Feedback Networks and Perceptual Learning

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Perceptual Learning refers to the continuous improvement of performance that follows practice in a perceptual task. Valid external feedback has been shown to enhance perceptual learning (Herzog & Fahle 1997). Here we used functional magnetic resonance imaging to identify cortical and subcortical regions that are activated when negative or positive external feedback is given during perceptual learning. We measured brain activity before and after extensive training of an orientation discrimination task with valid trial-wise external feedback (EF), enabling us to compare post and pre-training activity in regions activated by positive and negative EF.
The results reveal two distinct networks. Positive EF engages the posterior and anteriorcingulate cortex, superior frontal gyrus, ventral striatum, bilateral putamen (Globus pallidus), superior temporal gyrus, bilateral parahippocampal gyrus and posterior middle temporal gyrus (all $p < 0.05$ FWE-corrected). Negative EF engages the anterior cingulate cortex, bilateral insula, dorsolateral prefrontal cortex, substantia nigra, anterior thalamus and the right inferior parietal lobe (all $p < 0.05$ FDR-corrected).
Examining pre- and post-training differences of positive EF, we find that activity in the fusiform gyrus and orbitofrontal cortex decreases with training ($p < 0.01$ uncorrected), while for negative EF decreased activity is observed in the inferior and medial frontal gyrus ($p < 0.001$ uncorrected). Importantly, for both types of EF, we find increasing activity with training in the parahippocampal gyrus, a region involved in memory formation and the precuneus, which is associated with visuospatial processing.
We conclude that the cortical regions most affected by feedback-based perceptual training are not primary sensory regions but frontal and parietal networks.

P50: Cross-talk of mGluR5 and NMDA-receptor mediated by the mGluR5 positive allosteric modulator ADX-47273

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NMDA-receptors are crucially involved in cognitive functions. Studies in rat hippocampal slices have shown that activation of mGluR5 by a positive modulator in the presence of a subthreshold agonist concentration leads to a potentiation of NMDA-receptor mediated currents and phosphorylation of intracellular signalling proteins. This indicates a functional interaction between the mGluR5 and the NMDA-receptor in neurons. In the present study, this functional cross-talk between mGluR5 and NMDA-receptors was investigated in-vitro and in-vivo by using the selective mGluR5 positive modulator ADX-47273. By using FLIPR technology, ADX-47273 potentiated Ca2+ mobilization in rat primary neurons in the presence of a subthreshold concentration of the mGluR1/5 agonist DHPG with an EC50 of 0.28 $\pm$ 0.05 µM. NMDA-induced Ca2+-mobilization in rat primary neurons could be potentiated when neurons were pre-stimulated with 1 µM ADX-47273 in the presence of a subthreshold DHPG concentration. This cross-talk of the NMDA-receptor and mGluR5 in neurons could be blocked with the specific mGluR5 antagonist MPEP and the Src-family kinase inhibitor PP2. Furthermore, ADX-47273 elicited an enhancement of NMDA-receptor dependent long-term potentiation in rat hippocampal slices that could be reversed by MPEP. In-vivo, ADX-47273 showed a dose-dependent reduction of NMDA-receptor antagonist (ketamine) induced hyperlocomotion, indicating the mechanistic interaction of the NMDA-receptor and mGluR5. In summary, these findings further corroborate previous results on the functional cross-talk between the mGluR5 and NMDA-receptor, and thus, support the approach to address CNS diseases with cognitive impairments linked to NMDA-receptor hypofunction with mGluR5 positive allosteric modulators.

P51: The role of MAGUKs in cortical dependent memory formation and consolidation

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Complex functions of the central nervous system, such as learning and memory, are believed to result from the modulation of the synaptic transmission between neurons Signaling at synapses- key determinant of all aspects of brain function depends- on the activity of hundreds of synaptic proteins and their interactions. Although alterations in receptor density mediated by the insertion, lateral mobility, removal, and recycling of receptors are extensively studied, the dynamics and regulation of intracellular scaffolding proteins have only recently begun to be examined. More than just 'scaffold,' receptor associated proteins in synapses have been shown to provide a number of signaling roles. Membrane associated guanylate kinases (MAGUKs), including PSD-95, PSD-93, SAP-102, and SAP-97 represent a growing super-family of multi-domain proteins. Similarities in protein-protein interactions, functional overlapping and in glutamate receptor trafficking are observed among MAGUKs. Neural models of learning and memory, long term potentiation, and long term depression have shown the importance of MAGUKs in both AMPA&NMDA receptors dependent forms of synaptic plasticity. However, their functional roles in learning and memory in vivo have only begun to be understood, as our lab recently showed the induction of PSD-95 following novel taste in the relevant cortical area, the gustatory cortex. Moreover, this increase was necessary for memory consolidation but not retrieval. The aim of my research is to study the differential role of the MAGUKs in learning and memory and in regulating NMDARs function following sensory learning. Towards this end, we will examine the spatial and temporal expression patterns of the four MAGUKs and their associations with NMDARs in the gustatory cortex following both positive and negative forms of taste learning paradigms. We will use methods ranging from selective shRNA mediated knockdown, knockout mice via imaging and electrophysiology up to the behaving animal in order to make specific predictions about MAGUKs role in the molecular mechanisms underlying cognition.

P52: ERK2 activation in the Amygdala and Hippocampus following a reminder cue of an underwater trauma

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Persistent re-experiencing is a core symptom in posttraumatic stress disorder (PTSD) which includes elements of recurrent and intrusive recollections. Such intrusive recollections are believed to often be triggered by reminder cues associated with the traumatic event (DSM-IV, 1994). In this regard, mediating the formation and recollection of memories and particularly emotional ones, can partially be attributed to the activation of the Amygdala and the Hippocampus. Therefore, the present study examined the impact of exposure to the context (i.e. reminder cue) of a stressful experience (i.e. underwater trauma) on the activation of basolateral amygdala (BLA) and hippocampal formations (CA1, Dentate Gyrus) in the adult' rat brain. Rats were first exposed to underwater trauma and 24 hours later were re-exposed to the context of the trauma. 30 min following the context re-exposure rats were decapitated and the hippocampus (CA1, DG) and BLA brain reigns were harvested for further analysis. Phosphorylation of the extracellular signal-regulated kinase (ERK2) was used as a biochemical marker for the activation, following re-exposure, of the relevant brain regions. Significant increase in activation of ERK2 in the BLA was found following an exposure to the underwater trauma and 24 hours later to a reminder cue. Additionally, preliminary results point to an activation of the hippocampus regions, but this activation seem to differ both between the different formation regions and between re-exposed and un-exposed rats.

P53: Inhibition of protein kinase Mzeta and its effect on long-term potentiation in the dentate gyrus of freely moving rats

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Long-term potentiation (LTP) is defined as a long-lasting increase in the efficacy of synaptic transmission after brief high-frequency stimulation of afferent fibers and it has been used as a cellular model of learning and memory. LTP is defined as an increase in afferent synaptic strength but studies in the dentate gyrus (DG) often only analyzed the neuronal output, the population spike amplitude (PS) instead. The latter was thought to mimic the synaptic response. We have developed a method to simultaneously record the field excitatory post-synaptic potential (EPSP) and the PS in the dentate gyrus of freely moving rats. This procedure allowed us to measure the synaptic and the neuronal response at their place of generation. We have further used a technology of intrahippocampal injection of drugs for a better analysis of local events during DG-LTP. It has been suggested that the atypical protein kinase M zeta (PKMzeta) is required for prolonged phases of LTP. Therefore we have investigated if a specific stimulation protocol to induce L-LTP in the DG of freely moving rats also requires PKMzeta-activity. We have intrahippocampally injected myr-ZIP (a specific PKMzeta-inhibitor) 60 min after the induction of LTP. This fully prevented synaptic LTP measured at the synaptic sites, i.e. the EPSP-LTP. PS-potentiation was however not affected. This result suggests that PKMzeta is indeed required for L-LTP as defined as a synaptic change in efficacy after a brief tetanus of afferent fibers. However, it was not fully effective in influencing the PS-LTP suggesting a different regulation of excitability changes during LTP and synaptic events after the application of the PKMzeta-inhibitor. Therefore, two independent information storage mechanisms can be induced by LTP-induction as previously suggested (Andersen et al., 1980;Bliss and Lomo, 1973).

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P54: Deficit in learning under stress following viral vector-mediated CRF knock-down

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Stress is known to both triggers psychopathologies (e.g. depression, PTSD) and to affect learning and memory. At the physiological level, Corticotropin-Releasing Factor (CRF) plays a crucial role in mediating the stress response, by initiating the activation of hypothalamo-pituitary-adrenal axis (HPA axis), but also by modulating activity in various brain areas. This modulation is adaptive following mild and acute stress, but the excessive activation of the CRF system and the HPA axis may initiate stress-related pathologies, in part by involving aberrant learning. The objective of this work is to study the involvement of the CRF system in the interaction between learning and memory processes and stress-related disorders. We have used viral vector injection to chronically modulate HPA axis function, by up-regulating or down-regulating the CRF expression in the paraventricular nucleus (PVN). The two-way shuttle avoidance task (TWSA) was chosen to assess learning and memory processes under stressful conditions. This task is particularly relevant as it allows the study of two specific conditions. Under a controllable condition, animals learn to shuttle from one side to the other to avoid electrical foot shock by responding to a tone (the conditioned stimulus [CS]). However, under uncontrollable conditions, the CS remains fear-evoking since the rat behavior has no effect on shock presentation (Ilin and Richter-Levin, 2009). Our first results showed that the down-regulation of CRF expression in the PVN decreased the number of avoidance responses in a single session of the two-way shuttle avoidance task compared to control rats, suggesting dampened learning abilities in CRF KD rats. However, with respect to the effect on HPA axis activity, both control and treated rats exhibited the same increase of corticosterone blood level after the TWS conditioning session. We continue to examine the impact of manipulating CRF expression on learning under stress.

P55: Dopaminergic and cholinergic neuromodulation of novelty processing in humans

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Theoretical models and animal research suggest that both neurotransmitters dopamine and acetylcholine play an important role in encoding novel information. Direct evidence in humans, however, is still missing. Here, we used functional magnetic resonance imaging in combination with either dopaminergic or cholinergic neuropharmacology in a paradigm that allowed us to detect brain regions that are involved in novelty processing. As a main finding we can show that, in contrast to placebo, both levodopa (dopamine precursor) and galantamine (acetylcholinesterase inhibitor) differentially modulate novelty signals in the mesolimbic system (including substantia nigra / ventral tegmental area and medial temporal lobe regions) and the basal forebrain region. Therefore, our results directly support the possibility that novelty signals in the human mesolimbic system and basal forebrain involve dopaminergic and cholinergic neuromodulation.

P56: Effects of electrical stimulation of the Nucleus accumbens (Nacc) core and shell on voluntary ethanol intake in bulbectomised rats

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Bilateral removal of the olfactory bulbs is a validated animal model in depression research. It was previously shown that voluntary ethanol intake is increased in bulbectomised rats, which might be due to the addictive drug having less rewarding effects. Clinical studies have shown that deep brain stimulation of the Nacc might be an option in the treatment of chronic resistant alcoholism. The mechanisms underlying the anti-addictive effectiveness of deep brain stimulation are little understood. Relevant animal models are needed to study these mechanisms. To further elucidate the merit of the bulbectomy model, we studied the effect of electrical stimulation of the Na core and shell on voluntary ethanol intake.
Bulbectomised rats were offered water, 5%, and 10% ethanol solutions in a free-choice experiment. Compared with sham-operated animals, intake of 5% ethanol was increased and after a certain period bulbectomised animals switched to 10%. Intake of ethanol was negligible in sham-operated rats. Stimulation of the Nacc core significantly decreased ethanol intake in bulbectomised rats. When stimulation was terminated, ethanol intake returned to pre-stimulation values. Obviously, the effect was not persistent. Moreover, the anti-addictive effect seems to be region-specific. Stimulation of the Nacc shell had different effects. The Nacc core and shell have different connectivity with other brain areas. Interestingly, other studies demonstrated different effects of stimulation of the Nacc core and shell on long-term potentiation in the hippocampal dendrite area.
The results of our study clearly show that voluntary ethanol intake in bulbectomised rats might be a relevant tool for the study of the mechanisms underlying electrical stimulation effectiveness.

P57: Maximize success or minimize failure: individual achievement orientation modulates responsiveness to positive or negative reinforcement

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Instrumental learning is a basic mechanism in the shaping of human behaviour and cognition. However, concepts from differential psychology suggest that individuals could differ as to whether they are more motivated and learn more successfully by the anticipation of success (positive reinforcement) or prevention of failure (negative reinforcement).
The current behavioral study with 46 adults (25 male/ 21 female) used an incidental visual memory paradigm to investigate whether positive and negative feedback differentially modulate encoding success in different personality types. Relevant personality dimensions (e.g. achievement orientation: promotion oriented vs. prevention oriented) were assessed via questionnaires. In the encoding phase, subjects had the task to decide whether there was a human being in a picture or not. In half of the trials, a cue preceded the picture indicating whether successful task performance led to a gain of 50 cent (reward cue) or avoiding the loss of 50 cent (punishment cue) or had no consequence. In the other half, pictures were presented without a cue to explore whether anticipation intensified reward-related memory effects. Subjects received feedback after each stimulus and were informed on their current account status. The ratio between positive and negative feedback was fixed (60:40). Recognition was assessed immediately or three weeks after encoding.
In the overall sample, we found that positive and negative reinforcement both improved memory performance. When the pictures were presented without an anticipatory cue, negative reinforcement actually increased encoding success to a greater extent than positive reinforcement. As expected, individuals who scored high on prevention orientation (above the 75th percentile) showed the highest recognition rate for pictures in punishment trials with or without a cue, in which they could avoid monetary loss. Assuming that better memory performance in context of a reward paradigm is associated with an increase in activation of the dopaminergic reward network, our findings suggest that subjective value of a reinforcer could drive the dopaminergic response.

P58: Mechanisms for regulation of brain mitochondria by extramitochondrial Ca2+ as new targets of neurodegeneration

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Due to complex interactions between mitochondria and other cell compartments there are diverse possibilities for involvement of mitochondria in the pathophysiology of neurodegeneration (1). Recently we detected at isolated muscle mitochondria of R6/2 mice an increased sensitivity of OXPHOS against Ca2+-stress (2). Therefore we systematically investigated the role of cytosolic Ca2+ (Ca2+cyt) for the regulation of OXPHOS at isolated brain mitochondia of normal and transgenic animals as models of the neurodegenerative diseases Huntington, Parkinson and Alzheimer. In contrast to the textbooks we found that Ca2+cyt fully regulates the active respiration of brain mitochondria using the substrates -glycerophosphate on demand on the actualαglutamate/malate and also energy requirements. This occurs via the Ca2+cyt-stimulation of the glutamate aspartate carrier (aralar) and the mitochondrial -glycerophosphate dehydrogenase. Both enzymes have regulatory Ca2+α binding sites on the mitochondrial surface (in the intermembrane space) and are main constituents of the malat-aspartat-shuttle and the -glycerophosphate-shuttle, respectively. Activity of both shuttles isα reversibly and effectively regulated by Ca2+cyt in the range of physiological Ca2+cyt-concentrations between 50 and 300 nM Ca2+cyt. (3-5).
Brain mitochondria of transgenic animals were investigated with specific respirometric protocols (6). Active glutamate respiration of brain mitochondria from different transgenic Huntington animals was lower and inhibition by Ca2+-overload started at lower Ca2+cyt compared to the -synuclein miceαcontrols. Similar results were obtained with transgenic (Parkinson) and also at preliminary measurements of Alzheimer mice with Aß42-pathology.
-glycerophosphate dehydrogenase there are furtherαBesides aralar and proteins (porin, MgATP-carrier, Ca2+-uniporter, permeability transition pore) on the mitochondrial surface with assumed or confirmed regulatory Ca2+-binding sites. Therefore, we hypothesize that the cytotoxic -Synuclein, Aß42) can interact with theseαproteins (Huntingtinexp, Ca2+-binding sites, disturbing the normal interactions between mitochondria and Ca2+cyt which consequently causes mitochondrial dysfunction, energetic depression mitochondrial cell death and atrophy (1-5).

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P59: Behavioral tagging and capture: the impact and the role of neuromodulatory and glutamatergic innervation on hippocampus-dependent memory formation

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It is widely accepted that distinct hippocampus-dependent memory consolidation requires the synthesis of plasticity-related proteins (PRPs). These PRPs are generally synthesized by a proper salient experience that will be finally remembered. However, we have recently shown that an inconsequent event unable to be remembered (weak Inhibitory avoidance training: IA) can also use PRPs, provided by another associated event (exploration to a novel open field: OF), in order to stabilize its mnemonic trace for a long period of time. This process, named "behavioral tagging", depends on the setting of a local learning tag by the inconsequent event IA and also on the synthesis of PRPs induced by the associated event OF, that will later be captured at the tagged sites (Moncada and Viola, 2007).
It is also well established that long-term memory (LTM) formation for different learning tasks, including OF and IA, is affected by drugs acting on glutamatergic and catecholaminergic neurotransmitter systems. The infusion of agonists or antagonists into different brain structures can either positively or negatively modulate LTM formation. However, the cellular mechanisms underlying these effects are still unidentified. In other words, the specific role of each of these systems in LTM formation remains unknown. We suggest, that one reason for this is that common studies on memory consolidation have been undertaken using strong salient trainings, which can simultaneously trigger tag setting and PRPs synthesis processes, precluding the identification of the specific role (tag setting or PRPs synthesis) of each of the neurotransmitter systems.
Here, we use a combined pharmacological approach with different behavioral tagging-protocols of associative interactions of OF on IA and its impact on LTM formation. Our hypothesis is that IA sets a behavioral tag whereas OF induces PRP-synthesis. Then, specifically interfering with dopaminergic D1/D5, β-adrenergic or glutamatergic NMDA receptor function in dorsal hippocampus before IA or OF training sessions, we could dissect the role of these systems in the one or the other event. We show that neuromodulatory receptors are required to induce the PRP-synthesis necessary for IA-LTM consolidation, while NMDA-receptor activation seems to have a dual function, i.e. it is required for the setting of the IA-learning tag and PRP synthesis. We further show that the tag-setting-machinery also involves the activation of CAMKIIα and PKA but not ERK 1/2. These results support our earlier cellular data obtained in hippocampal brain slices in vitro.

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P60: Unexpected delay and omission of a feedback lead to equally strong brain activity

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Feedback is essential for any communication and is used to adjust one´s own behaviour in a dialog situation. When communicating with a machine, it is important to receive immediate feedback about the registration of an action (e.g. a button press). If this is not the case, such a human-computer dialog may fail or is at least annoying for the user. In the current study, we investigated the effects of delayed and omitted feedback on fMRI activation in comparison to immediate feedback.
Participants performed an auditory categorization paradigm, in which they had to decide whether the pitch of frequency-modulated tones was rising or falling. Independent of the correctness of the participants response they received an immediate visual feedback in form of a green checkmark in 76% of the cases. Thus, the feedback only indicated that a button press was registered. In 12% of all trials, the feedback was delayed by 500 ms and in another 12% the feedback was omitted.
Omitted compared to immediate feedback activated a network of brain regions including the posterior medial frontal cortex (pMFC), right dorsolateral prefrontal cortex (dlPFC), bilateral anterior insula/ inferior frontal gyrus (aI/GFi) and inferior parietal lobe (Lpi). A decrease in activation was observed in the anterior and posterior cingulate cortex. The effects on activation in all these regions seem to be evoked by higher attentional demands and/or adjustments in action control. Unexpectedly, a short delay in feedback produced essentially the same pattern and degree of activation as the omission of feedback even in those subjects who reported not to have noticed the delay. This finding emphasizes the importance of immediate feedback in human-computer interaction. Furthermore, we observed specific modulation of BOLD response in the dorsal striatum and the ventral tegmental area/substantia nigra which suggests that brain regions typically involved in reward processing are already activated by neutral feedback.

P 61: Assessing the feedback dependence of dopaminergic involvement in information-integration learning

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The dopaminergic system plays a crucial role in reward-based learning in animals (Schultz, 2006). In humans it has mainly been studied using gambling paradigms with the reward being earnings in money (e.g. Smith et al. (2009)). However, it was also claimed to participate in learning when only cognitive feedback is provided (Aron et al., 2004). We therefore conducted two experiments to assess the feedback dependence of dopaminergic involvement in an information-integration category learning task (Ashby and Maddox, 2005).

Methods

In the first experiment (Daniel and Pollmann, 2010) two parallel versions of the task were developed. The same subjects performed both task versions, receiving monetary reward in one version and only information about the correctness of their response in the other version. Functional imaging data was acquired after subjects were trained. In the second experiment an observational version of the same task was used in which subjects passively observed examples for each category in a learning phase. They then completed the same task as in the first experiment without ever receiving feedback. Functional imaging data was acquired for each subject during a naïve session and after extensive training.

Results

In our first experiment similar activations in the dopaminergic system were observed in both task versions with the Nucleus accumbens being activated in response to the receipt of both cognitive positive feedback and monetary reward compared to negative feedback. However, as the only significant difference, activation in the Nucleus accumbens was more pronounced when subjects expected monetary reward compared to cognitive feedback. This activation difference was higher in those subjects who applied an information-integration strategy instead of a suboptimal rule-based strategy. We also observed dopaminergic activations in the second experiment where feedback was never provided. Activation in the Nucleus accumbens decreased with training in the observational phase. In the test phase higher activations for correct than incorrect answers were observed in the Nucleus accumbens and the putamen, while higher activations for incorrect than correct answers were observed in the midbrain and medial prefrontal areas.

Conclusions

Our results indicate that the dopaminergic system is involved in information-integration category learning independently of the type of reward, monetary or cognitive. The Nucleus accumbens, however, responded more strongly to positive incentive of an expected reward. The dopaminergic system also responded in the absence of external feedback. These activations can be interpreted to contribute to learning via internal feedback signals from self-monitoring.

P62: Quantitative proteomic analysis of synaptic protein expression in punishment-motivated learning

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The molecular synaptic mechanisms underlying auditory discrimination learning in mice are largely unknown. Therefore, we have designed a proteomic study in a paradigm based on punishment for false decisions. Mice were trained in a shuttle box to discriminate between a rising and a falling frequency-modulated tone. To avoid mild foot-shock, the mice had to learn to cross a hurdle in response to the falling tone. False alarms and misses were avenged by a mild foot shock. After different numbers of training sessions, postsynaptic densities (PSD) were enriched from 4 different brain areas, namely auditory cortex, hippocampus, striatum and prefrontal cortex. Synaptic protein expression patterns obtained from trained mice, naive mice, tone-treated controls and foot shock treated animals were compared. MS-based quantification was performed by means of ICPL-quadruplex label technology (Serva, Germany). Every labelled sample assortment was digested with trypsin or GluC-endopeptidase, respectively. Resulting complex peptide mixtures were separated into 20 fractions by Isoelectric Focussing (IEF) in first dimension and by nano-reversed phase HPLC as second dimension. Nano-HPLC was directly coupled via an online-nanospray source to an ETD II-Iontrap mass spectrometer. Obtained MS/MS-data sets of four independent replicates were compiled in a Proteinscape database (Bruker, Germany), searched with the Mascot algorithm and relative expression levels were calculated using the WarpLC software package (Bruker, Germany). Obtained data sets were analysed by discrete mathematic algorithms followed by the ExPlain algorithm and the Transpath database (BioBase, Germany), which maps regulated proteins to known pathways and finally calculates upstream molecules which might serve as key nodes.
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P 63: Dissociating reward- and feature-related top-down biasing of sensory selection in visual cortex

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Attention can be drawn by a sudden onset of task irrelevant visual stimulation – an observation referred to as attentional capture. It turns out that attentional capture is not entirely automatic, but contingent on top-down expectations, e.g., on the degree to which features of a sudden onset stimulus match the set of task-relevant descriptions of the target (contingent attentional capture). While top-down settings may refer to a set of target-defining features (object color), they may also refer to the more general behavioral relevance of an object, e.g. whether it is associated with reward or whether it provides information important for directing future behavior. Considerable neurophysiological evidence indicates that top-down selection of relevant features is mediated by increasing the gain of sensory processing in extrastriate visual cortex. Here we use magnetoencephalographic recordings in human observers to investigate whether top-down settings due to reward-relevance (monetary reward) produce a similar biasing of sensory processing in extrastriate cortex. To avoid confounding reward- and target-related control settings we use an experimental design that guarantees that top-down settings defining the target feature do not overlap with the settings defining reward-relevance. We observe that under conditions of moderate reward-expectation (Experiment 1), contingent attentional capture by task-relevant features (color) is associated with a selective enhancement of the neuromagnetic response between 180-280 ms in posterior ventral extrastriate cortex. No such enhancement is seen in response to reward-relevant features. Increasing the expected amount of reward (Experiment 2) does not change the picture: contingent attentional capture by task-relevant features, but not by reward-relevant features, is associated with an enhanced response in extrastriate visual cortex. Reward-relevant features, instead, produce a delayed reduction of the neuromagnetic response when reward expectations are high. The data of the reported experiments together indicate that while reward-relevance (when sufficiently high) entails top-down modulatory impact on sensory processing in extrastriate visual cortex, it does not arise as automatic gain-bias analogous to what is seen for task-relevant features.

P64: Glutamatergic and resting-state functional connectivity correlates of severity in major depression - the role of pregenual anterior cingulate cortex and anterior insula

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Glutamatergic mechanisms and resting-state functional connectivity alterations have been recently described as factors contributing to major depressive disorder (MDD). Furthermore, the pregenual anterior cingulate cortex (pgACC) seems to play an important role for major depressive symptoms such as anhedonia and impaired emotion processing. Anhedonia a clinical core symptom in MDD characterised by the patients inability to experience pleasure and there it is regarded a main focus of impaired reward processing in depression. It is reliably present in severely depressed patients and may serve as a crucial target in the process of therapeutic learning and restructuring neagative biased thoughts, expectations and experience.
To further investigate the neurobiological underpinnings of the predescribed relationship of glutamatergic deficiency, anhedonia and abnormal functional responses in fMRI studies (Walter et al 2009),. we investigated 22 MDD patients and 22 healthy subjects using a combined magnetic resonance spectroscopy (MRS) and resting-state functional magnetic resonance imaging (fMRI) approach. Severity of depression was rated using the 21-item Hamilton depression scale (HAMD) and patients were divided into severely and mildly depressed subgroups according to HAMD scores. Because of their hypothesized role in depression we investigated the functional connectivity between pgACC and left anterior insular cortex (AI). The sum of Glutamate and Glutamine (Glx) in the pgACC, but not in left AI, predicted the resting-state functional connectivity between the two regions exclusively in depressed patients. Furthermore, functional connectivity between these regions was significantly altered in the subgroup of severely depressed patients (HAMD > 15) compared to healthy subjects and mildly depressed patients. Similarly the Glx ratios, relative to Creatine, in the pgACC were lowest in severely depressed patients (Horn et al 2010).
These findings support the involvement of glutamatergic mechanisms in severe MDD which are related to the functional connectivity between pgACC and AI and depression severity and provide evidence for a more complex network disturbance which also may explain the disintegration of AI from cognition related dorsofrontal networks.

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P65: High field fMRI reveals thalamocortical integration of segregated cognitive and emotional processing in mediodorsal and intralaminar thalamic nuclei

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A core system of human behaviour, reliebaly, but inversely, impaired in unipolar and bipolar depression, is responsible for processing sexually relevant information. As a multidimensional stimulation, aspects of reward, salience and cognitive control of behaviour have to be orchestrated by distinct, yet interacting cortical and subcortical systems, which have been poorly understood in humans.
Thalamocortical loops, connecting functionally segregated, higher order cortical regions and basal ganglia, have been proposed not only for well described motor and sensory regions, but also for limbic and prefrontal areas relevant for affective and cognitive processes. These functions are however more specific to humans, rendering most invasive neuroanatomical approaches impossible and transspecies translations difficult. Non invasive imaging of functional neuroanatomy using fMRI in contrast allows the development of elaborate task paradigms capable of testing the specific functionality proposed for these circuits. Until recently, spatial resolution largely limited anatomical definition of functional clusters at the level of distinct thalamic nuclei. Since these seem crucial not only for the distinction of cognitive and limbic loops but also for detection of their functional interaction during cognitive-emotional integration we applied high resolution fMRI on 7 Tesla.
Using an event related design we could isolate thalamic effects for preceding attention as well as experience of erotic stimuli. We demonstrate specific thalamic effects of general emotional arousal in mediodorsal nucleus and effects specific to expectancy and preceding attention in intralaminar centromendian/parafascicular complex. These thalamic effects were paralleled by specific coactivations in the head of caudate as well as segregated portions of rostral or caudal cingulate cortex and anterior insula supporting distinct thalamo-striatocortical loops. In addition to predescribed effects of sexual arousal in hypothalamus and ventral striatum, high resolution fMRI could extent this network to paraventricular thalamus encompassing laterodorsal and parataenial nuclei.
We could lend evidence to segregated subcortical loops which integrate cognitive and emotional aspects of the human reward system involved during processing of sexual information, elaborating its hedonic content and adapting attentional response elicited by the high salience of these stimuli. Such high resolution approach not only allows for monitoring of disturbances of involved subprocesses but is also of crucial importance for any invasive therapeutic intervention in reward related dysfunctions.

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Metzger C, Eckert U., Steiner J., Sartorius A., Stadler J., Tempelmann C., Speck O.
Bogerts B., Abler B., Walter M. High field fMRI reveals thalamocortical integration of segregated cognitive and emotional processing in mediodorsal and intralaminar thalamic nuclei in revision

P66: Behavioral and histological evaluation of Ethanol effects on reactivated fear conditioning processes on male rat

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Ethanol impairs acquisition of memory and at post-training either enhances or impairs learning. Little is known about the effect of ethanol on consolidated memories. Adult male Wistar rats were trained in a fear conditioning system using Two 1 s, 0.6 mA shock with an interval of 180s. 24 h later rats were returned to the chamber for 120s. Immediately after reactivation were injected with ethanol (0.5, 1, 1.5 mg/kg) or Saline. 1, 7 and 14 days after reactivation, rats were returned to the context for 5 min. Seconds of freezing (absence of all movement except respiration) were scored. Findings indicated that ethanol at a dose of 1.5 mg/kg significantly impaired recall of memory only in the first test. In the second experiment, after test 1 animals were anesthetized with sodium pentobarbital and perfused transcardially with phosphate buffer (10 min) and 4% paraformaldehyde (15 min). The brains were postfixed in phosphate-buffered 4% paraformaldehyde (24 h) and 30% sucrose (72 h). 5-µml sections were stained with cresyl violet. The density of CA1 and CA3 pyramidal and DG granule cells of ethanol group was decreased ($p < 0.01$) compared with control group respectively 43.7%, 35.8%, and 37.8.The data demonstrate that ethanol exposure impairs postretrieval processes via decreasing the density of CA1, CA3 and DG cells.

Impressum

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