



Annual Meeting
of the
Swiss Society for Neuroscience



Saturday March 26th 2011

Zentrum für Lehre und Forschung,
University Hospital Basel
Hebelstrasse 20, 4031 Basel

Program & Abstracts

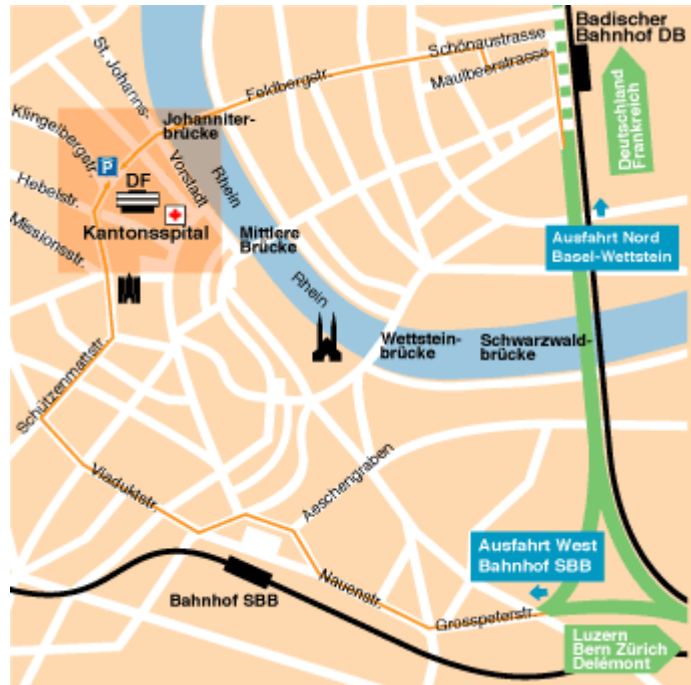
Direction to Zentrum für Lehre und Forschung (ZLF) of the Department of Biomedicine (DBM), University Hospital Basel

By train:

Take Bus number 30 at the train station Basel SBB and exit at station „Bernoullianum“.

By car:

Highway Basel City, then follow direction University Hospital (Universitätsspital). Parking possible in Parking City.



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Zentrum für Lehre und Forschung (ZLF)
Dep. of Biomedicine (former DF)
University Hospital

Bus 30 (from train station)



Annual Meeting of the Swiss Society for Neuroscience

March 26th 2011

**Zentrum für Lehre und Forschung
University Hospital Basel**

Organizing Committee

Pico Caroni, Chairman

Andreas Papassotiropoulos

Peter Scheiffele

Andreas Lüthi

Dominique De Quervain

Daria Knoch

Simone Grumbacher

Catherine Alioth

Logistics

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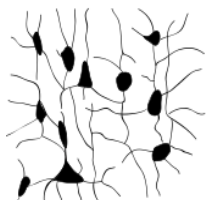
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Annual Meeting of the Swiss Society for Neuroscience

26th March 2011

ZLF, grosser und kleiner Hörsaal, Hebelstrasse 20, 4056 Basel

Program

08:30 Registration and poster setup

09:30 Welcome and Opening Remarks Nicole Schaeren-Wiemers, President SSN

09:40-10:25 Plenary Lecture 1

Pier Vincenzo Piazza, Bordeaux

Drugs or individuals? Fundamentals of a general theory of addiction

10:30-11:45 Parallel Symposia

Symposium 1: Cognition

Chaired by: Andreas Papassotiropoulos, Basel

Olaf Blanke, Lausanne

Neuroscience of the first-person perspective

Patrik Vuilleumier, Geneva

From vision to social neuroscience

Dominique de Quervain, Basel

Stress, genes and memory

Symposium 2: From Circuits to Behaviour

Chaired by: Pico Caroni, Basel

German Sumbre, Paris

Visual processing in the zebrafish larva

Botond Roska, Basel

The busy life of neural circuits in the retina

Hanns Ulrich Zeilhofer, Zurich

Inhibitory interneurons in spinal pain processing

11:45-14:00 Poster Session with Lunch

13:00-13:30 SSN Business Meeting: Chaired by: Nicole Schaeren-Wiemers

- Election of President-elect

- Welcome of the new president of the SSN Esther Stöckli

14:00-15:15 Parallel Symposia

Symposium 3: Genetics and Cell Biology of Neurodevelopmental Disorders

Chaired by: Peter Scheiffele, Basel

Thomas Bourgeron, Paris

How to get a social "synaptic" network in the brain: Insights from the genetics of autism spectrum disorders

Dominique Muller, Geneva

Alteration of synaptic network development by the mental retardation gene PAK3

Claudia Bagni, Leuven/Rome

mRNA metabolism and spine dysfunctions in Fragile X syndrome and autism spectrum disorder

Symposium 4: Learning and Memory

Chaired by: Andreas Lüthi, Basel

Ad Aertsen, Freiburg

From networks to networks of networks

Richard Hahnloser, Zurich

How the songbird brain listens to and evaluates its own songs

Christian Lüscher, Geneva

Network adaptations underlying compulsive drug seeking

15:30-16:15 Plenary lecture 2

Silvia Arber, Basel

Precision and function of neuronal circuits controlling motor behavior

16:15-16:25 Award Ceremony Best publication award, Volker Henn best poster price, Honorary member

16:25-16:45 Coffee Break

16:45-18:15 15th Anniversary Symposium: "Opportunities and Challenges for Swiss Neuroscience"

Chaired by: Esther Stoeckli

Martin Schwab (Zurich)

Pierre Magistretti (Lausanne)

Yilmaz Aysim (SNF)

Stephanie Clarke (Lausanne, SNF)

18:15 Closing remarks Esther Stöckli, incoming President

Summary 2011

A. Development of the Nervous System

- A2 Cellular changes underlying the normal postnatal development of the amygdala: a stereological study in monkeys.**
Loïc Chareyron, Pamela Banta Lavenex, David Amaral, Pierre Lavenex
-
- A3 Prenatal vitamin C deficiency leads to persisting hippocampal atrophy in the postnatal guinea pig**
Lucile Vogt, Pernille Tveden-Nyborg, Janne Gram Schjoldager, Natalie Jeannet, Stine Hasselholt Andersen, Maya Paidi, Stephan Christen, Jens Lykkesfeldt
-
- A4 Molecular effects of serotonin dysregulation in cortical interneuron migration**
Sarah Frazer, Alexandre Dayer
-
- A5 Ca²⁺ channels mediate inhibition of Purkinje cell dendritic growth after mGluR1 stimulation**
Olivia S. Gugger, Joseph P. Kapfhammer
-
- A6 Monitoring the effects of serotonin on migrating cortical interneurons using calcium imaging**
Nicolas Hurni, Alexandre Dayer
-
- A7 Semaphorin6B is required for rostro-caudal guidance of postcommissural axons**
Irwin Andermatt, Esther Stoeckli
-
- A8 Role of the 5-HT_{3A} receptor in cortical interneuron migration**
Sahana Murthy, Orbicia Riccio, Sandrine Rutz, Alexandre Dayer
-
- A9 Development of RNAi vectors eliciting cell type-specific, traceable gene knock down in the neural tube**
Nicole Wilson, Esther Stoeckli
-
- A10 Functional development of large-scale sensorimotor cortical networks in the brain**
Charles Quairiaux, Pierre Mégevand, Jozsef Z Kiss, Christoph M Michel
-
- A11 Excess of serotonin affects pyramidal neuron migration**
Moritz Jacobshagen, Orbicia Riccio, Alexandre Dayer
-
- A12 Monosynaptically-restricted Transsynaptic Viruses Reveal Distributed Nature of Premotor Spinal Interneurons and Synaptic Specificity of Cholinergic Partition Cells**
Anna Stepien, Marco Tripodi, Silvia Arber
-
- A13 Local slow-wave sleep: a marker of the maturation of specific performance skills in children**
Salome Kurth, Maya Ringli, Anja Geiger, Monique LeBourgeois, Oskar Jenni, Reto Huber
-

A14 Targeted electroporation of defined lateral ventricular walls: a novel and rapid method to study fate specification during postnatal forebrain neurogenesis.

María Eugenia Fernández, Simona Croce, Camille Boutin, Harold Cremer, Olivier Raineteau

A15 Role of the transcriptional factor Sox4 in Schwann cell development

Luca Bartesaghi, Estelle Arnaud, Roman Chrast

A16 Decline in progenitor diversity in the primate lateral ventricle

Kasum Azim, Stefan Zweifel, Fabienne Klaus, Kazuaki Yoshikawa, Irmgard Amrein, Lutz Slomianka, Olivier Raineteau

A17 Molecular Controls over the Modality-Specific Development of Thalamocortical Connectivity

Gabrielle Pouchelon, Denis Jabaudon

A18 Sleep EEG topography during development reveals sex differences.

Maya Ringli, Salomé Kurth, Oskar Jenni, Reto Huber

A19 Relationship between sleep slow wave activity and cortical maturation in rats

Nadja Olini, Salomé Kurth, Reto Huber

A20 Successful long term storage of expanded inner ear stem cells

Amir Mina, Stefano Di Santo, Angélique Ducray, Andreas Raabe, Hans R. Widmer, Pascal Senn

B. Molecular and Cellular Mechanisms: Cell-Cell Interaction

B1 Mapping hippocampal astrocyte calcium responses to single CA1 pyramidal neuron stimulation using light-activated channelrhodopsin-2

Yann Bernardinelli, Chris Salmon, Emma V. Jones, W. Todd Farmer, David Stellwagen, Keith K. Murai

B2 Localization of endogenous morphine in brain cells

Alexis LAUX, Arnaud H MULLER, Elise GLATTARD, Dominique AUNIS, Pierrick POISBEAU, Yannick GOUMON

B3 Optogenetic study of the local endogenous oxytocin release effects in the central amygdala neuronal populations.

Alexandre Charlet, Marios Abatis, Sophie Knobloch, Lena Hoffmann, Marina Eliava, Sergey Khrulev, Martin Schwarz, Peter Seeburg, Valery Grinevich, Ron Stoop

B4 Integration of new neurons in the adult hippocampus : in vitro synaptogenesis

Julie Sandell, Nicolas Toni

C. Molecular and Cellular Mechanisms: Signaling

C1 Ca²⁺ channels mediate inhibition of Purkinje cell dendritic growth after mGluR1 stimulation

Olivia S. Gugger, Josef P. Kapfhammer

- C2 CaV3.3 is the principal sleep pacemaker calcium channel**
Simone Astori, Ralf Wimmer, Corrado Corti, Mauro Corsi, Haydn Prosser, Nicolas Liaudet, Andrea Volterra, John P. Adelman, Anita Lüthi
-
- C3 Orexin-A inhibits NMDA receptors activity at rat mossy fiber synapses depending on time-of-day.**
Martina Perin, Fabio Longordo, Anita Lüthi
-
- C4 Promoting oscillatory activity in the nucleus reticularis thalami consolidates NREM sleep**
Ralf D. Wimmer, Chris T. Bond, John P. Adelman, Paul Franken, Anita Lüthi
-
- C5 Does the myelin and lymphocyte protein MAL play a functional role in intracellular Schwann cell signalling?**
Daniela Schmid, Nicole Schaeren-Wiemers
-
- C6 The functional role of the raft proteins MAL and PMP22 in the initiation of peripheral myelination**
Thomas Lazzati, Daniela Schmid, Thomas Zeis, Nicole Schaeren-Wiemers
-
- C7 GABAB receptors are targeted to proteasomal degradation via interaction with the AAA-ATPase SUG-1**
Khaled Zemoura, Thomas Grampp, Dietmar Benke
-
- C8 Paracrine factors secreted by Endothelial Progenitor Cells support viability of neuronal cells**
Di Santo Stefano, Ducray Angélique, Stefanie Seiler, Mina Amir, Raabe Andreas, Widmer Hans Rudolf
-
- C9 HIF-1 stabilization supports cultured dopaminergic neurons**
Nicole Porz, Angelique Ducray, Stefano Di Santo, Andreas Raabe, Hans R. Widmer

D. Molecular and Cellular Mechanisms: Learning and Memory

- D1 Circuit Mechanism of Fear Memory Formation in Auditory Cortex**
Johannes J. Letzkus, Steffen B.E. Wolff, Philip Tovote, Elisabeth M.M. Meyer, Julia Luedke, Andreas Luthi
-
- D2 Notch1 ablation induces molecular changes in plasticity genes that contribute to memory formation.**
Lavinia Alberi, Ramy Badie, Nicholas Gaiano
-
- D3 RSK2 affects neuronal development and synaptic activity through PLD1**
Mohamed-Raafet AMMAR, Yann Humeau, Nicolas Vitale
-
- D4 Genome-wide profile of H4K5 acetylation for fear memory-regulated genes**
C. Sehwan Park, Hubert Rehrauer, Isabelle Mansuy

E. Neural Excitability Synapses: Functional Aspects

E1 High-efficiency Channelrhodopsins for fast neuronal stimulation at low light levels

Philipp Schoenenberger, André Berndt, Peter Hegemann, Thomas G. Oertner

E2 Modulation of the GABAergic system in the basolateral complex of the amygdala: Action of the anxiolytic drug Etifoxin

Alexandre Zeitler, Pierrick Poisbeau, Pascal Darbon

F. Brain Metabolism and Homeostasis

F1 Regulation of cortical interneuron function by metabolic substrates

Luigi Bozzo, Jean-Yves Chatton

F2 Sensory stimulation alters the expression of cardiac troponin C, PACAP, and NPAS4 in the adult mouse barrel cortex

Christine Savary, Nathalie Wenger, Hubert Fiumelli, Jean-Luc Martin, Urs Albrecht, Egbert Welker

F3 The RNA-binding protein RBM3 is involved in hypothermia induced neuroprotection

Sophorn Chip, Andrea Zelmer, Cordula Nitsch, Sven Wellmann

F4 Cerebral metabolic compartmentation determined by high resolution in vivo ¹³C NMR spectroscopy

João MN Duarte, Bernard Lanz, Rolf Gruetter

G. Cognitive and Behavioral Neuroscience

G1 Development of a screening device for assessing visual attention in occupational health practice

Marino Menozzi, Esther Baumer

G2 Insulin resistance, hypertension and Attention Deficit Hyperactive Disorder: is there a link?

Edna Grünblatt, Jasmin Bartl, Andreas Borst, Diana-Iulia Iuhos, Peter Riederer, Melita Salkovic-Petrisic, Susanne Walitza

G3 Spontaneous brain activity engenders perception and determines discrimination sensitivity

Fosco Bernasconi, Aurelie Manuel, Micah M. Murray, Lucas Spierer

G4 Discrete stages in the development of hippocampus-dependent spatial memory in children.

Farfalla Ribordy, Pierre Lavenex, Pamela Banta Lavenex

G5 The right dorsolateral prefrontal cortex prevents post-error slowing

Aurélie Manuel, Francisco Bravo, Roland Vocat, Ayse At, Gilles Pourtois, Lucas Spierer

G6 Right DLPFC and VMPFC orchestrate normative decision-making

Thomas Baumgartner, Daria Knoch, Philine Hotz, Christoph Eisenegger, Ernst Fehr

- G7 Neural correlates of birdsong variability in different social contexts**
Jürgen Kornfeld, Andreas Kotowicz, Joshua Herbst, Richard Hahnloser
-
- G8 The role of single-trial, episodic multisensory learning in unisensory object discrimination**
Antonia Thelen, Céline Cappe, Micah Murray
-
- G9 Impact of emotion, sleep and re-test on face-name association learning.**
Rosanna De Meo, Claire Bindschaedler, Mélanie Aeschlimann
-
- G10 Dissociation between frontal and parietal lesion in spatial neglect patient**
Arnaud Saj, Vincent Verdon, Claude-Alain Hauert, Patrik Vuilleumier
-
- G11 Tracking the brain dynamics of gut hormone influences on food image discrimination in normal-weight women across hunger states**
Claudia V. Lietti, Jeremy Saugy, Léonie Egli, Vanessa Campos, Luc Tappy, Vittorio Giusti, Micah M. Murray, Ulrike Toepel
-
- G12 Neural control of a motor pattern in zebrafish: an optogenetic analysis**
Otto Fajardo, Peixin Zhu, Rainer W. Friedrich
-
- G14 Functional connectivity of the resting brain in obsessive compulsive disorder**
Hamdi Eryilmaz, Martin Desseilles, Pierre Maquet, Dimitri Van De Ville, Sophie Schwartz
-
- G15 Upside Down: Visual-vestibular conflict induces illusory changes in the experienced direction of the first-person perspective**
Christian Pfeiffer, Roberto Martuzzi, Julio Duenas, Roger Gassert, Olaf Blanke
-
- G16 Dopaminergic modulation of learning about a person's trustworthiness**
Andreas Pedroni, Christoph Eisenegger, Christian Zehnder, Ernst Fehr, Daria Knoch
-
- G17 Age dependent decrease of adult hippocampal neurogenesis in the wild South African Namaqua rock mouse is gender-specifically regulated**
Nicole Cavegn, Dominik Menges, Mashudu Phalanndwa, Christian T. Chimimba, Irmgard Amrein
-
- G18 Physiological correlates of subjective time: evidence for the temporal accumulator hypothesis**
Domenica Bueti, Emiliano Macaluso
-
- G19 Effects of blue-enriched polychromatic light on ocular and electroencephalographic correlates of human alertness and melatonin**
Sarah Chellappa, Roland Steiner, Peter Blattner, Peter Oelhafen, Thomas Götz, Christian Cajochen
-
- G20 Born with an Ear for Dialects? Structural Plasticity in the Expert Phonetician Brain**
Narly Golestani, Cathy Price, Sophie Scott
-
- G21 Single administration of levodopa modulates reward sensitivity but not self-control in a social decision making task**
Matthias Hartmann, Andreas Pedroni, Christoph Eisenegger, Urs Fischbacher, Ernst Fehr, Daria Knoch

-
- G22 Identifying and exploiting the electrophysiology of illusory body parts ownership and motor imagery**
Nathan Evans, Olaf Blanke
-
- G23 Musical syntax processing as a function of musical expertise – Part 1: Spatio-temporal ERP analyses and source imaging.**
Clara E. James, Mathias S. Oechslin, Dimitri Van De Ville, François Lazeyras, Claude-Alain Hauert
-
- G24 Probabilistic reversal learning in mice: establishing a task and assessing serotonin effects using genetic and pharmacological methods**
Christian Ineichen, Simona Spinelli, Klaus-Peter Lesch, Erich Seifritz, Christopher Pryce
-
- G25 Prediction of exploratory decision-making from single-trial topographic EEG analyses**
Athina Tzovara, Micah M. Murray, Nicolas Bourdaud, Ricardo Chavarriga, José del R. Millán, Marzia De Lucia
-
- G26 Motor evoked potentials during repeated presentations of environmental sounds**
Nathalie Bourquin, Alexandre Simonin, Stephanie Clarke
-
- G27 Musical syntax processing as a function of musical expertise - Part 2: fMRI analyses**
Mathias S. Oechslin, Dimitri Van De Ville, Francois Lazeyras, Claude-Alain Hauert, Clara James
-
- G28 Effects of Pulse-Modulated Mobile Phone-Like Fields and Pulsed Magnetic Fields on the Human Sleep EEG**
Marc Schmid, Sarah Loughran, Manuel Murbach, Caroline Lustenberger, Niels Kuster, Peter Achermann
-
- G29 Temporal dynamics of brain activation of biologically-relevant stimuli**
Lore Legrand, Marzia del Zotto, Christelle Aubert, Vanessa Sennwald, Alan Pegna
-
- G30 Long – range integration of emotional prosody and spatial attention is underlined by amygdalo – orbitofrontal synchronization in humans**
Andy Christen, Lucas Tamarit, Laurent Spinelli, Margitta Seeck, Didier Grandjean
-
- G31 Eyes like it, brain likes it: Tracking the neural tuning of cultural diversity in eye movements for faces**
Junpeng Lao, Luca Vizioli, Sébastien Miellet, Roberto Caldara
-
- G32 Intermale aggression and coping style in RHA/RLA rats**
Tamara VAUDROZ, Laurence SEYNAEVE, Thierry STEIMER
-
- G33 Development of a mouse model for the study of specific and generalized “helplessness”, a major concept in depression**
Damiano Azzinnari, Tilo Gschwind, Hannes Sigrist, Irene Knuesel, Erich Seifritz, Christopher Pryce
-
- G34 Genome-wide Analyses of the Transgenerational Impact of Early Life Stress in Mice**
Johannes Bohacek, Guillaume Coiret, Osvaldo Mirante, A. Leonardo Iniguez, Guido Steiner, Carl Kashuk, Francesca Manuella, Katharina Gapp, Jean-Luc Moreau, Isabelle M. Mansuy
-

- G35 Secondary sexual traits in human male and female bodies: electrophysiological and behavioral studies.**
Marzia Del Zotto, Lore B. Legrand , Chiara Chilla, Sophie Nussbaum , Alan J. Pegna
-
- G36 Valid, sensitive, interpretable: A new approach to EEG analysis**
Armand Mensen, Ramin Khatami
-
- G37 Wake-up morning light improves cognitive performance after sleep restriction**
Virginie Gabel, Antoine Viola, Micheline Maire, Amandine Valomon, Caroline Reichert, Sarah Chellappa, Vanja Hommes, Christian Cajochen
-
- G38 Auditory Perception with Neuromorphic Chips**
Sadique Sheik, Giacomo Indiveri
-
- G39 Changes in sleep EEG at moderate altitude**
Katrin Stadelmann, Tsogyal D. Latshang, Christian M. Lo Cascio, Noemi Tesler, Anne-Christin Stoewhas, Malcolm Kohler, Konrad E. Bloch, Reto Huber, Peter Achermann
-
- G40 Distinction of posed and genuine emotional expressions under high and low task relevance**
Juliane Wilcke, Tracey McLellan, Lucy Johnston, Richard Watts, Lynden Miles
-
- G41 The Effects of Visual Feedback Manipulation in Virtual Reality on Cortical Activity: A Pilot Study**
Johannes Brand, Olivia Geisseler, Lisa Holper, Marie-Claude Hepp-Reymond, Manfred Morari, Daniel Kiper, Kynan Eng
-
- G42 Trait-like spindle activity, information processing speed and their association to sleep-dependent performance improvement**
Caroline Lustenberger, Angelina Maric, Roland Dürr, Peter Achermann, Reto Huber
-
- G43 Model-based analysis of learning and memory in a genome-wide association study**
Gediminas Luksys, Leo Gschwind, Christian Vogler, Angela Heck, Sandra Ackermann, Klara Spalek, Dominique de Quervain, Andreas Papassotiropoulos
-
- G44 Processing of subliminal and unattended stimuli: an ERP study**
Alan Pegna, Alexandra Darque, Lore Legrand, Marzia Del Zotto
-
- G45 Sensory Motor Training Station with ARMin Robot to Improve Hand Eye Coordination**
Katherine Grace August, Mathini Sellathurai, Saana Jenu, Marco Guidali, Daniel Bleichenbacher, Verena Klamroth-Marganska, Sergei Adamovich, Robert Riener
-
- G46 Novel object recognition test in tree shrew (*Tupaia belangeri*)**
Abbas Khani, Gregor Rainer
-
- G47 Circadian and homeostatic influences on sequence learning are affected by age**
Carolyn F. Reichert, Antoine Viola, Christina Schmidt, Kurt Kräuchi, Christian Cajochen
-

G48 Auditory sensory gating responses in adolescents with a high genetic risk for schizophrenia

Tonia A. Rihs, Juliane Britz, Miralena Tomescu, Vincent Rochas, Maude Schneider, Sarah Menghetti, Stephan Eliez, Christoph M. Michel

G49 Inter-individual differences in circadian rhythmicity: effects of age and PER3 polymorphism

Amandine Valomon, Antoine Viola, Christina Schmidt, Christian Cajochen

G50 Differences in anxiety/impulsivity and prefrontal cortex connectivity in the Roman High-(RHA) and Low-(RLA) Avoidance rats

Adrian Briner, Thierry Steimer, Alexandre Dayer, Laszlo Vutskits

G51 Probing the involvement of both hemispheres during early stages of word processing by event-related TMS

Vincent Rochas, Tonia Rihs, Alexis Hervais-Adelman, Gregor Thut, Christoph M. Michel, Theodor Landis

G52 Influence of odor in aversive conditioning: assessing affective preparedness in the olfactory system

Aline Pichon, Sylvain Delplanque, I. Cayeux, David Sander, Patrik Vuilleumier

G53 A novel, time-based non-matching to place protocol reveals short-term spatial memory deficits in monocarboxylate transporter MCT2 knockdown mice

Fulvio Magara, Camille Viviani, Luc Pellerin

H. System Neuroscience and Neuroinformatics

H1 Correlative microscopy of densely labeled projection neurons using neural tracers

Daniele Oberti, Moritz Kirschmann, Richard Hahnloser

H2 Dopamine innervation of Area 10 of prefrontal cortex in normal and MPTP treated macaques

Isabelle Spühler, Rita Bopp, Julien Vezoli, Henry Kennedy, Kevan Martin

H3 Local excitatory circuits of macaque Area 8A (Frontal Eye Fields)

John C Anderson, Nuno M daCosta, Henry Kennedy, Kevan AC Martin

H4 Dissecting the role of interneuron subtypes in fear learning: an optogenetic approach.

Steffen Benjamin Eggert Wolff, Cyril Herry, Ingrid Ehrlich, Philip Tovote, Stephane Ciochi, Christian Müller, Andreas Lüthi

H5 Optogenetic analysis of activity pattern readout in the zebrafish homolog of olfactory cortex

Peixin Zhu, Yan-Ping Zhang, Jennifer Shum, Francisca Blumhagen, Rainer W. Friedrich

H6 Canonical circuits in mouse auditory cortex

Marco Perrella, Nuno Maçarico da Costa, Kevan A.C. Martin

- H7 Encoding odors by spike packets sequences from ensemble of rate-invariant neurons in awake mice**
Olivier Gschwend Gschwend, Jonathan Beroud, Alan Carleton
-
- H8 Dense sensory input maps evoked by natural odorants in awake mice**
Roberto Vincis, Jonathan Beroud, Olivier Gschwend, Khaleel Baukhaurally, Alan Carleton
-
- H9 Temporal dynamics of spiking and LFP activity depend on CRT monitor refresh rate in tree shrew primary visual cortex**
Julia Veit, Anwesha Bhattacharyya, Robert Kretz, Gregor Rainer
-
- H10 Reconstruction of neuronal connectivity in the zebrafish olfactory bulb by 3D electron microscopy**
Adrian Wanner, Christel Genoud, Rainer Friedrich
-
- H11 Layer-specific cholinergic modulation in the tree shrew primary visual cortex**
Anwesha Bhattacharyya, Felix Biessmann, Julia Veit, Robert Kretz, Gregor Rainer
-
- H12 Measurements and learning experiments in a neuromorphic VLSI system.**
Guillaume Viejo, Giacomo Indiveri
-
- H13 Retinal and post-retinal contributions to the Quantum efficiency of the human eye.**
Gibram Mannaseh, Chloe de Balthazar, Bruno Sangunetti, Enrisco, Nicolas Gisin, Rolando Grave de Peralta, Sara Gonzalez
-
- H14 How the brain ultrastructure is altered by conventional EM preparation techniques**
Natalya Korogod, Christel Genoud, Anthony Holtmaat, Carl Petersen, Graham Knott
-
- I. Brain Imaging**
-
- I1 Impairment of prefrontal activation and connectivity during executive function in Parkinson's Disease: a combined fMRI/DTI study.**
Sandra E. Leh, Alain Ptito, Abbas Sadikot, Jenkai Chen, Marc Bohlken, Sonja Huntgeburth, Antonio P. Strafella
-
- I2 Localisation of epileptic generators with EEG-fMRI informed by EEG topographic maps**
Frédéric Grouiller, Rachel Thornton, Kristina Groening, Laurent Spinelli, Karl Schaller, Michael Siniatchkin, Louis Lemieux, Margitta Seeck, Christoph M. Michel, Serge Vulliémot
-
- I3 Sodium imaging: new strategies for optical probing of neural circuits.**
Christophe Lamy, Olivier Sallin, Jean-Yves Chatton
-
- I4 Functional mapping of cortical language areas with functional MRI in individual subjects**
Frédéric Grouiller, Mélanie Genetti, Karl Schaller, Laurent Spinelli, Margitta Seeck, Christoph Michel
-
- I5 Error processing and post error adjustment in a flanker task**
Yann Cojan, Camille Pigué, Patrik Vuilleumier
-

- I6 Human Primary Auditory Cortex Follows the Shape of Heschl's Gyrus**
Sandra E. Da Costa, Wietske Van der Zwaag, José P. Marques, Richard S. Frackowiak, Stephanie Clarke, Melissa Saenz
-
- I7 Hemispheric asymmetry of cortical terminations of the human arcuate fasciculus: an in vivo probabilistic tractography study**
András Jakab, Ervin Berényi, Péter Katona, Mónika Béresova, Gábor Székely
-
- I8 Content-specific memory reactivations depend on medial temporal lobe integrity**
Christoph Hofstetter, Chiara Cristinzio, Yann Cojan, Margitta Seeck, Patrik Vuilleumier
-
- I9 Speech in Noise: Neural substrates of challenging speech perception with and without supporting semantic context**
Alexis Hervais-Adelman, Jonas Obleser, Sophie Scott, Narly Golestani
-
- I10 Modulation of auditory spatial attention through emotion: an fMRI auditory dot-probe study**
Ceravolo Leonardo, Frühholz Sascha, Grandjean Didier
-
- I11 Electrophysiological evidence for ventral stream deficits in schizophrenia**
Gijs Plomp, Maya Roinishvili, Eka Chkonia, George Kapanadze, Andreas Brand
-
- I12 Manipulating Visual Perception with Real-Time fMRI-based Neurofeedback Training**
Frank Scharnowski, Chloe Hutton, Oliver Josephs, Nikolaus Weiskopf, Geraint Rees
-
- I13 Neural face coding is shaped by race**
Luca Vizioli, Fraser Smith, Junpeng Lao, Lars Muckli, Roberto Caldara
-
- I14 Electrical Neuroimaging of Early Sensory Processing in First-Episode Psychosis**
Jean-François Knebel, Lucas Spierer, Philippe Baumann, Carina Ferrari, Andrea Polari, Tanja Teichmann, Kim Q. Do, Philippe Conus, Micah M. Murray
-
- I15 Emotion in dreams predicts amygdala response to aversive stimuli**
Virginie Sterpenich, Catherine Laty, Sophie Schwartz
-
- I16 Opposing consequences for memory stability when reactivated during waking and sleep**
Susanne Diekelmann, Christian Büchel, Jan Born, Björn Rasch
-

J. Disorders of the Nervous System: Basic Mechanisms

- J1 Development of high-density scalp somatosensory evoked potential recordings in macaque monkeys**
Anne-Dominique Gindrat, Charles Quairiaux, Juliane Britz, Florian Lanz, Christoph M. Michel, Eric M. Rouiller
-
- J2 In utero exposure to cocaine impairs postnatal synaptic maturation of glutamatergic transmission in the VTA.**
Camilla Bellone, Manuel Mameli, Christian Lüscher
-

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- J3 Synergistic neurorestorative effects of angioglioneurin Intracerebral administration and environmental enrichment in developing rats**
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Abstracts 2011

A. Development of the Nervous System

A2 Cellular changes underlying the normal postnatal development of the amygdala: a stereological study in monkeys.

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Abnormal development of the amygdala has been linked to several neurodevelopmental disorders, including schizophrenia and autism. However, the postnatal development of the amygdala is not easily explored at the cellular level in humans. We therefore performed a stereological analysis of the monkey amygdala in order to characterize the cellular changes underlying its normal structural development in primates. We counted the number of neurons, astrocytes and oligodendrocytes, measured the size of neuronal somas and the volume of the main amygdala nuclei at different postnatal ages. The lateral, basal and accessory basal nuclei exhibited the same developmental pattern, with a large increase in volume between birth and three months of age, followed by a slower growth until at least 5-9 years. In contrast, the central nucleus was already highly developed at birth and increased significantly in volume only between one year and 5-9 years of age; the medial nucleus was highly developed at birth and exhibited only a marginal increase in volume to reach adult levels. Quantitative analyses of different cell types revealed that neither neuronal soma size nor the numbers of neurons or astrocytes changed during postnatal development. In contrast, there was a large increase in oligodendrocyte number and myelination, which was associated to an increase in amygdala volume after one year of age. Interestingly, at birth, the paralaminar nucleus contained a large pool of immature neurons that developed gradually into mature neurons, leading to a late increase in volume of this nucleus. Our findings revealed that different amygdala nuclei have distinct developmental profiles and that the amygdala is not fully mature until young adulthood. We discuss how pathogenic factors at different postnatal ages might lead to the abnormal development of distinct amygdala circuits, thus contributing to different neurodevelopmental disorders affecting amygdala structure and functions in humans.

A3 Prenatal vitamin C deficiency leads to persisting hippocampal atrophy in the postnatal guinea pig

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BACKGROUND. The brain maintains one of the highest concentrations of vitamin C in the body, but its exact role in brain function is not well understood. However, in a recent study in guinea pigs, we showed that postnatal depletion of vitamin C is associated with a reduction of the number of neurons in the hippocampus and impaired learning and memory performance in the Morris water maze test.

OBJECTIVE. In the present study, we wanted to see whether vitamin C depletion in newborn guinea pigs affects postnatal hippocampal neurogenesis, and whether this effect is also observed when animals have been vitamin C-deficient during gestation.

METHODS. Eighty pregnant mothers were weight-stratified at gestational day 18 into two groups and either received 900 or 100 mg of vitamin C per kg diet. Newborn pups were weaned within the first few days after birth and were either fed with the same diet their mothers received during pregnancy, or switched from high to low or low to high, overall resulting in 4 different treatment groups: 900/900, 100/100, 900/100 and 100/900 mg of vitamin C per kg pre-/postnatally. Male pups received 5 consecutive injections of BrdU between postnatal day (P)5 and P9 to assess proliferation of precursor cells on P10 and survival/migration/maturation of newborn cells on P27. Female animals were sacrificed at 2 months after birth (postnatal depletion was not performed). Ascorbate levels were determined in plasma and one of the brain hemispheres, and the other hemisphere was used for immunohistochemistry and hippocampal volume determination.

RESULTS. Similar to prolonged postnatal vitamin C deficiency, brain ascorbate levels were severely depleted in pups born from mothers fed with the low vitamin C diet. In contrast, repletion of deficient animals after birth with the high vitamin C diet resulted in rapid normalization of brain ascorbate levels. Neither prenatal nor postnatal vitamin C deficiency resulted in decreased hippocampal proliferation at P10 or decreased survival, migration, or maturation of newborn cells at P27. However, pre- but not postnatal depletion was associated with an approx. 10-15% lower hippocampal volume, an effect that could not be reversed by postnatal repletion with vitamin C, even for 2 months.

CONCLUSIONS. Prenatal vitamin C deficiency causes retardation of postnatal hippocampal development in guinea pigs.

A4 Molecular effects of serotonin dysregulation in cortical interneuron migration

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In humans, monkeys and rodents, reduced expression and function of the serotonin transporter (SERT) is associated to a range of psychiatric disorders. The pathological effects of SERT hypofunction is likely caused by a developmental excess of serotonin on cellular processes involved in circuit formation. Among these processes, cortical interneuron migration has been previously shown in the lab to be affected by an excess of serotonin. In this project, we aim to study the molecular pathways that are disrupted in cortical interneurons by an excess of serotonin. Two complementary approaches will be used to block SERT: 1) Generation of constitutive SERT-ko mice that express GFP specifically in cortical interneurons. 2) Chronic administration of a selective serotonin reuptake inhibitor (fluoxetine) in GAD65-GFP+ mice during pregnancy. GAD65-GFP labeled interneurons will be FACS-sorted, RNA will be extracted and gene-expression changes will be assessed using DNA microarrays and confirmed by qPCR. Target genes dysregulated in SERT-ko mice and in fluoxetine-injected mice will be identified. The function of target genes on interneuron migration and differentiation will be tested using gain/loss of function approaches in cortical slices and in vivo. This project will lead to the identification of new molecular targets induced by serotonin dysregulation in developing cortical interneurons using a cell-specific in vivo approach.

A5 Ca²⁺ channels mediate inhibition of Purkinje cell dendritic growth after mGluR1 stimulation

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The development of a neuronal dendritic tree is modulated by signals from afferent fibers as well as by an intrinsic program. We have previously shown that chronic activation of class I metabotropic glutamate receptors (mGluR1) in organotypic cerebellar slice cultures severely inhibits the growth and development of the Purkinje cell dendritic tree. The signaling events underlying these effects remain largely unknown. P/Q-type Ca²⁺ channels have been shown to play a role in Purkinje cell spontaneous activity which emerges in parallel with their dendritic tree. T-type Ca²⁺ channels colocalize with mGluR1 and are potentiated upon mGluR1 activation. We have studied whether pharmacological blockade of P/Q-type and/or T-type Ca²⁺ channels would attenuate dendritic reduction induced by chronic activation of mGluR1. Purkinje cells were grown in slice cultures for 10 days, thereof 7 days in the presence of the mGluR1 agonist DHPG. These treatments resulted in a strong reduction of the size of the dendritic tree. Alternatively, Purkinje cells were treated in the same way with DHPG over 7 days, but in the presence of the P/Q-type Ca²⁺ channel inhibitors -Agatoxin IVA and -Conotoxin MVIIC and with the T-type Ca²⁺ channel inhibitor Mibefradil. Purkinje cell dendrites were analyzed at the end of the culture period. Purkinje cells in cultures receiving the P/Q- and T-type Ca²⁺ channel inhibition along with DHPG showed a significantly increased branching and average size compared to the ones in cultures receiving only DHPG. Thus, simultaneous inhibition of T- and P/Q-type Ca²⁺ channels partially antagonized the dendrite-reducing effect of chronic mGluR1 activation. Purkinje cells in cultures which received either the T- or the P/Q-type Ca²⁺ channel inhibitors along with DHPG showed no significant changes in dendritic tree size compared to the ones in cultures receiving only DHPG. These findings suggest that both T- and P/Q-type Ca²⁺ channels are involved in mGluR1 signaling leading to the inhibition of dendritic growth in cerebellar Purkinje cells.

A6 Monitoring the effects of serotonin on migrating cortical interneurons using calcium imaging

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Cortical circuits are formed by two major neuronal cell types, inhibitory GABAergic interneurons and excitatory glutamatergic pyramidal neurons, which both migrate during development to reach the neocortex following distinct migratory routes. The proper migration of cortical interneurons is critical for normal brain function. Previous work in the lab has revealed that serotonin could modulate the migration of cortical interneurons while they invade the cortical plate. In this study we aim to determine whether the effect of serotonin on neuronal migration is dependent on the modification of calcium transients in migrating interneurons. To perform calcium imaging, GAD65-GFP+ interneurons in cortical slices will be loaded with Fura-2 a calcium-sensitive dye allowing the monitoring of calcium signals in GFP+ cells. Our preliminary results indicate that serotonin affects calcium transients in migrating interneurons. Using agonists for the different serotonin receptors we are currently exploring the molecular mechanisms that mediate the effects of serotonin on cortical interneuron migration. These studies will allow us to better understand the intracellular down-stream effectors that mediate the effects of monoamines on neuronal migration.

A7 Semaphorin6B is required for rostro-caudal guidance of postcommissural axons

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The Semaphorins form a large family of repulsive and attractive axon guidance proteins. More than 30 members divided into eight classes are known. In contrast to the well studied secreted class-3 Semaphorins, much less is known about the role of transmembrane class-6 Semaphorins. Because of its spatial and temporal expression pattern, we tested for a role of *Sema6B* in commissural axon guidance. In the developing chicken spinal cord the dorso-lateral population of commissural neurons sends axons to the floor plate, where they cross the ventral midline. Subsequently, axons grow rostrally along the longitudinal axis of the spinal cord in close contact with the contra-lateral floor-plate border. When *Sema6B* was knocked down by *in ovo* RNAi, axons often stalled within the floor plate and lacked an instructive signal directing them rostrally along the contralateral floor-plate border. Post-crossing commissural axons randomly chose to grow either rostrally or caudally. The expression pattern of PlexinAs, known binding partners of class-6 Semaphorins, suggested an interaction between *Sema6B* on commissural axons and PlexinA1 and A2 expressed by floor-plate cells. Indeed, downregulation of these two Plexins at the midline resulted in stalling of commissural axons within the floor plate. These results suggest that *Sema6B* in commissural neurons acts as a receptor that mediates a guidance effect of midline-derived PlexinAs.

A8 Role of the 5-HT3A receptor in cortical interneuron migration

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The migration of cortical interneurons plays a critical role in the assembly of cortical circuits and could be involved in the developmental origin of psychiatric disorders. About 70% of cortical interneurons are generated in the medial ganglionic eminences (MGE) of the subpallium, whereas about 30% are generated in the caudal ganglionic eminences (CGE). Understanding the molecular mechanisms that differentially regulate the migration of MGE-derived versus CGE-derived interneurons is a fundamental question. The 5HT3A receptor is specifically expressed in CGE-derived interneurons as early as E14.5 but not in MGE-derived interneurons. Furthermore 5-HT3A knock-out mice have recently been shown to display an autistic-like phenotype. In this work, we aim to determine the role of the 5HT3A receptor in the migration of CGE-derived interneurons. To address this question, we have used time-lapse imaging at different developmental time points to monitor the migration of CGE-derived interneurons. We found that the application of a 5HTA receptor agonist has no effects on the migration of interneurons at E15.5 but stimulates the migration of interneurons at E18.5. These preliminary data indicate that the 5HT3A receptor could play a role in the migration of CGE-derived interneurons while they invade the cortical plate but not during the earlier phase of tangential migration. In our further studies we aim to use calcium imaging to further demonstrate the differential responsiveness of E15.5 versus E18.5 interneurons to 5HT3A activation. Finally, to study the role of the 5HT3A receptor in CGE-derived migration *in vivo*, we will use 5HT3A receptor knock-out mice as well as cell-specific 5HT3A receptor over-expression manipulations. These studies will allow us to understand the role of the 5-HT3A receptor in the assembly of neural circuits.

A9 Development of RNAi vectors eliciting cell type-specific, traceable gene knock down in the neural tube

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The pathfinding behaviour of commissural axons of the developing neural tube is one of the best studied model systems in axon guidance. Typically, the commissural axons express receptors or cell adhesion molecules that detect cues emanating from their intermediate target, the floor plate. To allow us to test the molecular and cellular interactions of novel axon guidance candidates, we report the design and synthesis of cell type-specific RNA interference constructs for use in the chick neural tube. The vectors are based on artificial derivatives of pri-miR-30 (Das et al, 2006). Cell type-specific promoters/enhancers drive the expression of a fluorescent protein marker, followed by the miR30-RNAi transcript (located within the 3'-UTR of the fluorescent protein). When electroporated into the developing neural tube, these vectors elicit cell type-specific, traceable gene knock down. Two genes are able to be targeted from a single RNAi vector, or they can be mixed prior to electroporation, to enable the simultaneous knock down of two or more genes in independent regions of the spinal cord (ie floor plate and commissural neurons). We have applied the new vectors to knock down several genes (Axonin1, Shh, Wnt7a, Glypican1) in proof-of-principle experiments. Not only do the vectors elicit dramatic knock down of gene expression (detectable by in situ hybridization and immunohistochemistry), but the level of knock down is sufficient to reproduce the expected guidance defects upon perturbation of genes with known axon guidance functions. All vectors express bright fluorescence to enable direct tracing of the cells experiencing knock down. In addition, we describe an in vitro method to rapidly assess the relative efficiency of new miRNAs against their target gene. The advancements of the in ovo RNAi technique that we describe will markedly enhance the biological validity, experimental precision and combinatorial possibilities of studies in RNAi, axon guidance and neural development.

A10 Functional development of large-scale sensorimotor cortical networks in the brain

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Large-scale neuronal networks integrating several cortical areas mediate the complex functions of the brain such as sensorimotor integration. Little is known about the functional development of these networks and the maturational processes by which distant networks become functionally connected. We addressed this question in the postnatal rat sensorimotor system. Using epicranial multi-electrode grids that span most of the cortical surface and intracortical electrodes, we show that sensory evoked cortical responses continuously mature throughout the first 3 weeks with the strongest developmental changes occurring in a very short time around postnatal day (P) 13. Before P13, whisker stimulation evokes slow, initially surface-negative activity restricted mostly to the lateral parietal area of the contralateral hemisphere. In a narrow time window of about 48 hours around P13, a new early sharp surface-positive component emerges that coincides with subsequent propagation of activity to sensory and motor areas of both hemispheres. Our data suggest that this new component developing at the end of the second week corresponds to functional maturation in superficial cortical layers and appears to be crucial for the functional associations in the large-scale sensorimotor cortical network. It goes along with the onset of whisking behavior as well as major synaptic and functional changes within the S1 cortex that are known to develop during this period.

A11 Excess of serotonin affects pyramidal neuron migration

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Serotonin (5-HT) is a neurodevelopmental signal that can regulate a variety of cellular processes involved in the formation of cortical circuits. The serotonin transporter (SERT) is a key molecule involved in the homeostasis of extra-cellular levels of serotonin. Genetic deletion of SERT in rodents leads to a state of increased levels of serotonin that affects neocortical circuit assembly such as barrel cortex formation. In this study, we investigated whether an excess of serotonin could affect the migration of neocortical pyramidal neurons. Using in utero electroporation combined to time-lapse imaging to specifically label and monitor pyramidal neurons during the late rodent embryonic period, we found that an excess of serotonin alters the radial migration of pyramidal neurons in a reversible manner. We next investigated whether the positioning of upper layer cortical neurons could be altered in vivo in the SERT knock-out mice, a mouse model with stress-related phenotypes. Our preliminary findings indicate that the distribution of electroporated pyramidal neurons is altered in the SERT knock-out mice. Taken together, these results indicate that an excess of serotonin can affect pyramidal neuron migration, a critical step in the assembly of neural circuits. These findings support the hypothesis that genetically driven variations in serotonin function could have detrimental effects on circuit formation and contribute to an increased vulnerability to psychiatric disorders.

A12 Monosynaptically-restricted Transsynaptic Viruses Reveal Distributed Nature of Premotor Spinal Interneurons and Synaptic Specificity of Cholinergic Partition Cells

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Movement is the behavioral output of neuronal activity in the spinal cord. Motor neurons are grouped into motor neuron pools, the functional units innervating individual muscles. Here we establish an anatomical rabies-virus based connectivity assay in early postnatal mice. We employ it to study the connectivity scheme of premotor neurons, the neuronal cohorts monosynaptically connected to motor neurons, unveiling three aspects of organization. First, motor neuron pools are connected to segmentally widely-distributed yet stereotypic interneuron populations, differing for pools innervating functionally-distinct muscles. Second, depending on subpopulation identity, interneurons take on local or segmentally-distributed positions. Third, cholinergic partition cells involved in the regulation of motor neuron excitability segregate into ipsilaterally and bilaterally projecting populations, the latter exhibiting preferential connections to equivalent motor neuron pools bilaterally. Our study visualizes the widespread yet precise nature of the connectivity matrix for premotor interneurons and reveals exquisite synaptic specificity for bilaterally projecting cholinergic partition cells.

A13 Local slow-wave sleep: a marker of the maturation of specific performance skills in children

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We recently showed that the topographical distribution of slow-wave activity (SWA, 1-4.5 Hz) in the sleep electroencephalogram (EEG) undergoes major changes during childhood. These spatial EEG changes follow a maturational 'posterior to anterior' course and parallel findings from anatomical and functional studies, suggesting SWA as a marker of cortical maturation. In a next step, we investigated the direct relationship of individual SWA topography and the maturation of specific performance skills.

All-night high-density sleep EEG (128 electrodes) in 63 healthy subjects (2-26y) were included in this analysis. In order to quantify performance skills, various tasks were carried out in subsets of individuals. Each task was z-scored and averaged within the categories 'simple motor', 'complex motor', 'rotation learning', 'language' and 'cognitive control'.

As expected, absolute SWA increased during childhood and decreased thereafter. Electrodes were co-registered with the subject's magnetic resonance image allowing us to define regions of interest based on Brodmann areas related to our performance skills. The spatial succession of these regions of interest reaching maximal SWA revealed a specific developmental pattern. We next defined an index for the individual's developmental stage based on this pattern. Finally, we correlated this SWA-derived developmental index with performance skills and found a significant relationship for 'complex motor ability' ($p=.0001$, $R^2=.25$) and 'rotation learning' ($p=.04$, $R^2=.11$).

These data propose sleep SWA as a marker of motor performance skills during development. The inverted U-shape of SWA across age may indicate cortical synaptic pruning and associated fine-tuning of local cortical functioning.

A14 Targeted electroporation of defined lateral ventricular walls: a novel and rapid method to study fate specification during postnatal forebrain neurogenesis.

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Background: Postnatal olfactory bulb (OB) neurogenesis involves the generation of granule and periglomerular cells by neural stem cells (NSC) located in the walls of the lateral ventricle (LV). Recent studies show that NSC located in different regions of the LV give rise to different types of OB neurons. However, the molecular mechanisms governing neuronal specification remain largely unknown and new methods to approach these questions are needed.

Results: In this study, we refine electroporation of the postnatal forebrain as a technique to perform precise and accurate delivery of transgenes to NSCs located in distinct walls of the LV in the mouse. Using this method, we confirm and expand previous studies showing that NSCs in distinct walls of the LV produce neurons which invade different layers of the OB. Fate mapping of the progeny of radial glial cells located in these distinct LV walls reveals their specification into defined subtypes of granule and periglomerular neurons.

Conclusions: All together, our results provide a baseline onto which future studies aiming at investigating the role of factors in postnatal forebrain neuronal specification can be compared. Targeted electroporation of defined LV NSC populations will prove valuable to study the genetic factors involved in forebrain neuronal specification.

A15 Role of the transcriptional factor Sox4 in Schwann cell development

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The differentiated Schwann cells can revert their phenotype and de-differentiate after a nerve injury or in demyelinating pathologies. The de-differentiation of mature Schwann cells is driven by the activation of multiple negative regulators of myelination including c-Jun, Notch, Sox-2 and Pax-3, all usually expressed in the immature Schwann cells and suppressed at the onset of myelination. In order to identify new negative regulators involved in the development of the peripheral nervous system (PNS) we analyzed the data from a previously performed transcriptional analysis of myelinating Schwann cells. Based on its transcriptional expression profile during myelination, Sox4, a member of the Sox gene family, was identified as a potential candidate. Previous studies demonstrated that prolonged Sox4 expression in oligodendrocytes maintains these cells in a premyelinating state, further suggesting its role as a negative regulator of myelination. Concomitantly, we observed upregulation of Sox4 mRNA and protein expression levels in the PNS of three different models of demyelinating neuropathies (Pmp22, Lpin1 and Scap KO). To better characterize the molecular function of Sox4, we used a lentiviral vector allowing Sox4 overexpression in cultured Schwann cells and in neuron-Schwann cell co-cultures. In parallel we generated two transgenic lines of mice in which the overexpression of Sox4 is driven specifically in Schwann cells by the promoter of Myelin Protein Zero. The preliminary data from these in vitro and in vivo experiments show that overexpression of Sox4 in PNS causes a delay in progression of myelination. While our data so far indicates that Sox4 acts as a negative regulator of Schwann cell myelination, we still need to clarify the underlying molecular mechanisms leading to this phenotype.

A16 Decline in progenitor diversity in the primate lateral ventricle

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The subventricular zone (SVZ) of the lateral ventricle (LV) of the forebrain is a niche of continuing neurogenesis throughout life in the mammalian central nervous system and is the primary source of newborn olfactory neurons. It appears to be a highly complex region in terms of the spatial distribution of defined progenitor pools through the rostro-caudal axis as well as the location of progenitors in distinct SVZ walls.

Estimates of the numbers and distribution of proliferating cells and migrating neuroblasts were performed in the mice and marmoset's forebrain, by Ki67 and doublecortin (DCX) staining, respectively. 3D reconstruction revealed important differences in migratory paths of progenitors and a decline in proliferating cells as well as migrating neuroblasts in primates. Next, the expression pattern of two transcription factors, i.e. Dlx2 and Tbr2 were studied in the mouse and marmoset LV. We show that in both species, these transcription factors were found to label separate, divergent lineages originating from the LV. 3D reconstructions confirmed the presence of lineage specific progenitors within distinct spatial regions of the LV in mice. Interestingly, the numbers of Dlx2+ progenitors was reduced in the SVZ of adult marmosets compared to the adult mouse, whilst Tbr2+ progenitors were undetectable in adult marmoset SVZ and only few detected in newborns.

Altogether, these findings highlight significant phylogenetic differences in progenitor's number and diversity in the adult LV and underline the need for careful assessment of neurogenesis in distinct mammalian species.

A17 Molecular Controls over the Modality-Specific Development of Thalamocortical Connectivity

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In the mammalian cerebral cortex, sensory inputs and motor output are processed in distinct specialized areas with unique anatomical and functional properties. Input to these areas is provided by neurons located in distinct sensory and motor nuclei of the thalamus, and a precise connectivity between the distinct subtypes of thalamic neurons and the cortex is critical to the proper development of sensory and motor areas. Here, we investigate the molecular mechanisms controlling the area-specific connectivity of distinct subtypes of thalamocortical neurons during development, using microarray gene expression analysis of populations of thalamic neurons projecting to the somatosensory cortex (in the VPM and POm thalamic nuclei), visual cortex (LGN nucleus) and motor cortex (VL nucleus) at critical stages of development in the mouse. This approach has enabled us to identify several novel neuron-type specific genes with mutually exclusive expression in distinct subtypes of thalamocortical neurons, whose functional characterization in the assembly of distinct sensory and motor circuits is currently underway. Together, these findings reveal novel molecular codes that uniquely identify distinct subtypes of thalamocortical neurons, and may determine their specific connectivity during forebrain development.

A18 Sleep EEG topography during development reveals sex differences.

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Objectives: Recently the topographical distribution of slow wave activity (SWA, 0.5-4Hz) in the sleep EEG was proposed to be a useful tool to uncover age-dependent differences in cortical maturation (Kurth et al., 2010). Here we asked, if potential sex differences can be detected in the SWA topography.

Methods: Sleep EEG was recorded in 11 boys (13.42±3.94) and 11 girls (13.4±3.88 years) using high-density EEG (128 electrodes). Additionally all electrodes were co-registered to each individuals magnetic resonance image. Mean SWA was calculated for the first 60 minutes of NREM sleep for each electrode and compared between males and females.

Results: The comparison of SWA topography revealed two major clusters of electrodes showing increased SWA in girls compared to boys, one located over the left frontotemporal (15%, $p=0.03$, unpaired t-test) and the other over the right parietotemporal (10%, $p=0.07$, unpaired t-test) cortex. The anatomical localization of these clusters revealed Brodmann area (BA) 22, BA 45 and BA 47 for the frontotemporal and BA 22 und BA 39 for the parietotemporal region – all areas involved in language processing.

Conclusion: The comparison of SWA topography in young females and males showed that girls exhibit higher SWA in areas known to serve language processing. Sex differences in language processing were also found in a fMRI study, where girls showed generally higher and more bilateral activation of linguistic areas during language processing (Bruman et al., 2008). These results support the usefulness of SWA topography to uncover anatomical differences.

A19 Relationship between sleep slow wave activity and cortical maturation in rats

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Slow wave activity (SWA) during non-rapid eye-movement sleep represents a well-established measurement for sleep need, which increases as a function of prior wakefulness (Borbely and Achermann 1999). Human data shows a prominent decrease in EEG slow wave activity during adolescence, which was proposed to reflect cortical maturation (Campbell and Feinberg 2009). However, no causal relationship between cortical maturation and sleep SWA has been shown. In this study we collected continuous EEG recordings in 11 male pre- and post pubertal Sprague Dawley rats (postnatal day 26 (P26) to 45 (P45)). During the experiment rats were individually housed and maintained on a 12hr:12hr light-dark cycle. EEG signals were filtered and subjected to a fast Fourier transform for 4-s epochs. Vigilance states were scored by visual inspection of 4-s epochs. In a first analysis only the first 3 hours of the light period were considered. The results show an increase of SWA in early pubertal rats up to P30 followed by a steady decline until rats enter adulthood (SWA in % of P30 \pm SE, P26: 75.5 \pm 5.2; P30: 100.0 \pm 0; P42: 60.3 \pm 15.2; t-tests $p(26/30) < 0.001$, $p(30/42) < 0.05$, $p(26/42) < 0.05$). The duration of wakefulness (preceding 12 hours dark period) increased from P26 to P42, and thus, does not explain the observed decrease of SWA between P30 and P42. In addition, a measurement of sleep continuity, the amount of brief awakenings, exhibits a similar time course as the trajectory of SWA. To test whether the manipulation of SWA during early development has an effect on cortical maturation we prevented the build up of SWA by means of caffeine (Schwierin, Borbely et al. 1996). Preliminary data shows that such a manipulation results in a delayed reduction of SWA during adolescence. We now investigate the anatomical and behavioural consequences of this promising observation.

A20 Successful long term storage of expanded inner ear stem cells

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Background. Inner ear stem cells are promising candidates for a potential future cell therapy for sensorineural hearing loss and could prove useful for cell biological and physiological studies, because they give rise to differentiated inner ear cell types in vitro. For optimum availability and as a basis for any transplantation program, cryopreservation of inner ear stem cells is a prerequisite. **Purpose.** To investigate the possibility of cryopreservation of inner ear stem cells. **Methods.** Stem cells were isolated from neonatal rat and human fetal inner ear and propagated in basal medium containing mitogens. Both dissociated cell suspensions and intact spheres were frozen down at -145°C in serum free medium containing 10% DMSO as a cryoprotectant for up to a three month duration. The number of spheres after thawing was assessed and compared to the number prior to freezing. Intact spheres were assessed for cell differentiation before freezing and after thawing. Further propagation and differentiation assay of the thawed spheres was attempted. **Results.** Both neonatal rat and human fetal inner ear derived spheres could be successfully frozen and thawed. Despite a significant decline in sphere numbers after thawing, the spheres of human and rat origin could be propagated and differentiated into inner ear cell types including hair cells and spiral ganglion neurons. **Conclusion.** Inner ear stem cells can be frozen and thawed before being, propagated and differentiated into inner ear cell types.

B. Molecular and Cellular Mechanisms: Cell-Cell Interaction

B1 Mapping hippocampal astrocyte calcium responses to single CA1 pyramidal neuron stimulation using light-activated channelrhodopsin-2

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Astrocytes respond to neuronal activation in vitro and in vivo with intracellular calcium elevations. These intracellular calcium changes enable astrocytes to modulate synaptic transmission and plasticity through a variety of mechanisms. However, the response pattern of astrocytes to single neuron depolarization events still remains unresolved. This information is critical for fully understanding the coordinated network of neuron-glia signaling that occurs in the brain. To address this question, we developed a system to map astrocyte calcium responses along apical dendrites of CA1 pyramidal neurons in hippocampal slices using single neuron stimulation with channelrhodopsin-2. This technique allowed selective neuronal depolarization without invasive manipulations that are known to alter calcium levels in astrocytes. Light-evoked neuronal depolarization was elicited and calcium events in surrounding astrocytes were monitored using the Calcium Orange-sensitive dye. Stimulation of single neurons caused calcium responses in populations of astrocytes along the apical axis of CA1 cell dendrites. Observed calcium responses were characterized by single events that were synchronized with neuronal stimulation or post-stimulus changes in calcium event frequency. Interestingly, although individual astrocytes near CA1 cells showed low ability to respond to repeated neuronal depolarization events, the fidelity of the response of the surrounding astrocyte population was remarkably accurate. Furthermore, the reliability of astrocyte responses were graded with respect to their location along the CA1 cell dendrite, with cells residing in the primary dendrite subregion being most responsive. This study provides a new approach for noninvasively mapping astrocyte calcium events through light-evoked neuronal activation and underscores the dynamic response behaviour of astrocyte ensembles to neuronal activity.

B2 Localization of endogenous morphine in brain cells

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Morphine, the principal active agent in opium, is not restricted to plants, but is also present in different animal tissues and cell types, including the mammalian brain. In mammals, endogenous morphine (EM) derives from the dopamine biosynthesis pathway. However, the role of brain EM is matter of debate and knowledge about its distribution is lacking. A straight forward approach to study the roles of EM and morphine-derived molecules in brain physiology is to examine in detail their localization in brain structures. First, a mass spectrometry approach confirms the presence of EM in mouse brain, but also, for the first time morphine-6-glucuronide and morphine-3-glucuronide. Secondly EM was quantifying in the mouse brain showing her presence at concentration ranging from 1.45 to 7.5 pmol/g. And finally a detailed immunohistochemical mapping of EM and its glucuronides in the adult mouse brain was performed showing EM presence in various structures including hippocampus, olfactory bulb, band of Broca, basal ganglia, cerebellum, areas not only involved in pain modulation. Interestingly we observed that morphine immunoreactivity is mainly present in GABAergic cells whereas it is surprisingly absent from dopaminergic cells and processes. Astrocytes were also labeled throughout the entire brain, in cell body, process, and astrocytic foot around blood vessels. To conclude, the presence of EM in brain regions not usually involved in pain modulation opens the exciting opportunity to extend the role and function of EM beyond analgesic functions a lead us to conclude that it has a specific function in neuromodulation and/or neurotransmission.

B3 Optogenetic study of the local endogenous oxytocin release effects in the central amygdala neuronal populations.

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Hypothalamic oxytocin (OT) acts centrally to mainly orchestrate social behaviors, enhancing trust and attenuating fear, but also reducing pain feeling. If its general function is now well referenced, the sites and cellular structures of OT release within the forebrain remain unknown. Here we gained genetic access to hypothalamic OT neurons in the rat by synthesizing recombinant adeno-associated virus under the control of OT promoter. These AAVs, injected in some hypothalamic nuclei, allowed us to study the connectivity of fluorescent OT neurons in the brain and to control their activity by optogenetic means and blue-light stimulation. We found OT fibers, and particularly axons, in many forebrain regions, including the central amygdala (CeA), a structure critically involved in OT-mediated suppression of fear and associated autonomic responses. In the CeA, we visualized monosynaptic axonal projections of magnocellular OT neurons and recorded OT-dependent electrophysiological responses to localized blue-light stimulation of channelrhodopsin-2-expressing OT fibers. Thus, the behavioural and autonomic effects of OT are mediated by its central release from long-range axonal projections.

B4 Integration of new neurons in the adult hippocampus : in vitro synaptogenesis

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1) FNS 2) UNIL

New neurons are continuously integrated into existing neural circuits in the adult dentate gyrus of the mammalian brain. What is the function of these new cells and how are they integrated? Nowadays, the role of adult hippocampal neurogenesis is still unclear even though increasing evidence suggests its involvement in hippocampus-dependent learning and memory. The integration of these newly generated neurons represents a unique form of plasticity in the hippocampus and result in a drastic remodeling of the adult circuitry. We recently showed, at the electron microscope level, that adult-born neurons preferentially contact pre-existing synapses, thereby forming multiple synapse boutons (MSB). To better understand how newborn neurons integrate in the hippocampus at the synaptic level, we will explore the morphological mechanisms of synaptogenesis in vitro and focus on MSB formation, stability and dynamics. First, to observe long-term synapse formation and stability we will use a co-culture system of primary neurons and adult hippocampal stem cell-derived neurons, tagged fluorescently with pre- and post-synaptic marker, and time-lapse imaging. Then, to explore the role of neuronal activity in MSB dynamics, we will use a technique of light-driven control of neuronal excitability based on Channelrhodopsin-2 expression. The combination of these techniques will enable us to study the role of neuronal activity on synaptic integration, MSB formation and new neurons maturation and survival.

C. Molecular and Cellular Mechanisms: Signaling

C1 Ca²⁺ channels mediate inhibition of Purkinje cell dendritic growth after mGluR1 stimulation

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The development of a neuronal dendritic tree is modulated by signals from afferent fibers as well as by an intrinsic program. We have previously shown that chronic activation of class I metabotropic glutamate receptors (mGluR1) in organotypic cerebellar slice cultures severely inhibits the growth and development of the Purkinje cell dendritic tree. The signaling events underlying these effects remain largely unknown. P/Q-type Ca²⁺ channels have been shown to play a role in Purkinje cell spontaneous activity which emerges in parallel with their dendritic tree. T-type Ca²⁺ channels colocalize with mGluR1 and are potentiated upon mGluR1 activation. We have studied whether pharmacological blockade of P/Q-type and/or T-type Ca²⁺ channels would attenuate dendritic reduction induced by chronic activation of mGluR1. Purkinje cells were grown in slice cultures for 10 days, thereof 7 days in the presence of the mGluR1 agonist DHPG. These treatments resulted in a strong reduction of the size of the dendritic tree. Alternatively, Purkinje cells were treated in the same way with DHPG over 7 days, but in the presence of the P/Q-type Ca²⁺ channel inhibitors -Agatoxin IVA and -Conotoxin MVIIIC and with one of the T-type Ca²⁺ channel inhibitors Mibefradil or NNC 55-0396. Purkinje cell dendrites were analyzed at the end of the culture period. Purkinje cells in cultures receiving the P/Q- and T-type Ca²⁺ channel inhibition along with DHPG showed a significantly increased branching and average size compared to the ones in cultures receiving only DHPG. Thus, simultaneous inhibition of T- and P/Q-type Ca²⁺ channels partially antagonized the dendrite-reducing effect of chronic mGluR1 activation. Purkinje cells in cultures which received either a T- or the P/Q-type Ca²⁺ channel inhibitors along with DHPG showed no significant changes in dendritic tree size compared to the ones in cultures receiving only DHPG. These findings suggest that both T- and P/Q-type Ca²⁺ channels are involved in mGluR1 signaling leading to the inhibition of dendritic growth in cerebellar Purkinje cells.

C2 CaV3.3 is the principal sleep pacemaker calcium channel

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Among the low-threshold Ca²⁺ channel family, the CaV3.3 channel encoded by the alpha11 or CACNA11 gene has been proposed to be involved in synchronized thalamocortical rhythms related to sleep. This hypothesis is based on the strong expression of CaV3.3 channels in the nucleus reticularis of the thalamus (nRt), a fundamental sleep pacemaker composed of a shell of GABAergic neurons interposed along the thalamocortical pathway. We here report the first characterization of a mouse mutant lacking the alpha11 gene and demonstrate the cellular basis for the essential role of CaV3.3 channels in generating sleep-related rhythms. Electrophysiological recordings were performed from thalamic neurons in acute slices from 3-4-week-old CaV3.3 KO mice and wild-type littermates. The lack of the alpha11 gene impaired repetitive oscillatory bursting in the low-frequency range (4-10 Hz) in nRt neurons, while sparing low-threshold burst discharge in adjacent thalamocortical (TC) neurons. Reciprocal synaptic interactions between nRt and TC neurons were strongly weakened, largely preventing the generation of synchronized network discharges in the spindle frequency range (10-12 Hz). The alpha11 gene accounts for the majority of the T-type Ca²⁺ current and is the dominant Ca²⁺ source for dendritic Ca²⁺ signals in nRt neurons, as revealed from Ca²⁺-imaging experiments performed in nRt cells infused with bis-fura-2 (1 mM). Thus, CaV3.3 channels are primarily responsible for sleep-related rhythmic activity in the nRt. The impact of CaV3.3 deletion on the electroencephalographic profile of CaV3.3 KO mice is currently being investigated.

C3 Orexin-A inhibits NMDA receptors activity at rat mossy fiber synapses depending on time-of-day.

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Orexins are neuropeptides synthesized by lateral hypothalamic neurons and released into numerous brain regions. Food intake, sleep-wake architecture, arousal and motivation are some of the major functions regulated by orexins. Interestingly, orexin receptors are also expressed in the hippocampus, but their roles in hippocampal functions are largely unknown. We have now identified a novel, specific inhibitory effect of orexin-A on NMDA-EPSCs at mossy fiber-CA3 synapses, the key entry site of hippocampus. Pharmacologically isolated NMDA-EPSCs were recorded from CA3 pyramidal cells in acute rat hippocampal slices (P21-P30). Mossy fiber origin was ascertained by >80% block of response with the mGluRII agonist DCG-IV (1 M). Orexin-A (100 nM, 5-10 min in bath) decreased NMDA-EPSCs to $55.6 \pm 6.8\%$ of control ($n=10$, $p<0.0005$) in a partially reversible manner ($73.2 \pm 7.4\%$ of control after 25 min wash-out, $n=10$, $p<0.05$). Orexin-A did not affect NMDA-EPSC amplitude in two other major excitatory hippocampal synapse types. Orexin-A effects were mediated postsynaptically, as they manifested on iontophoretically elicited NMDA-currents ($75.5 \pm 4.9\%$ of baseline, $n=6$, $p<0.005$).

Orexin-A levels in the cerebrospinal fluid (CSF) fluctuate with a diurnal rhythmicity. We explored whether a time-of-day variability of orexinergic functions could be observed at the cellular level. Bath application of orexin-A affected NMDA-currents in slices prepared during the rats' predominant resting time, when CSF orexin-A levels are low (~11 am) In contrast, in slices prepared during the active period (~6 am), when CSF orexin-A levels are high, orexin-A did not affect NMDA-currents ($95.0 \pm 5.1\%$ of control, $n=3$, $p>0.05$). In conclusion, orexin-A specifically and powerfully downregulates postsynaptic NMDA receptor function at mossy fiber synapses. Moreover, the orexinergic system appears to regulate information flow through select hippocampal pathways depending on time-of-day.

C4 Promoting oscillatory activity in the nucleus reticularis thalami consolidates NREM sleep

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The nucleus reticularis thalami (nRT) is known for its pacemaking function during oscillatory brain activity related to non-rapid eye movement sleep (NREMS). Intrinsic nRT oscillations are mediated through interplay of low-voltage activated (T-type) Ca^{2+} channels and small conductance type 2 (SK2) K^{+} channels. Loss of SK2 channel function impairs nRT oscillations and deteriorates NREMS quality (Cueni et al, 2008). We ask whether over-expressing SK2 channels (SK2OE) potentiates nRT oscillatory capacity and stabilizes NREMS. Whole-cell patch-clamp recordings were obtained in horizontal brain slices (300µm) from SK2OE and wildtype littermates (C57Bl/6J background; PND 25-34). Oscillatory nRT bursting was strengthened in SK2OE cells due to >2-fold greater SK2 currents while T-currents were unaltered ($p>0.05$). However, SK2OE cells had fewer action potentials (AP) per burst ($p<0.01$). In line with this, burst induced spontaneous IPSCs recorded in thalamocortical (TC) projection neurons, the target cells of the nRT, showed a diminished capacity to generate rebound APs in SK2OE neurons ($p<0.002$). Nonetheless, synchronized activity in nRT-TC circuits was strengthened in thalamic slices ($p<0.05$), indicating that synchronously bursting SK2OE nRT cells facilitated oscillatory network activity related to sleep oscillations. Spontaneous sleep-wake electroencephalogram (EEG) was monitored continuously for 48h. SK2OE mice spent less time in REMS ($p<0.05$) and more time in longer (>2min) NREMS episodes ($p<0.05$) during light periods. At NREMS-REMS transitions, SK2OE mice showed a slower drop of EEG delta power (0.5 - 4Hz) and a smaller peak in sigma power (11 - 15Hz; $p<0.05$). SK2OE increased single cell oscillatory capacity in the nRT, while compromising inhibitory output. Nonetheless, synchronized network activity appeared strengthened, which might have delayed the exit from nRT oscillatory bursting at NREMS-REMS transitions resulting in a consolidation of NREMS at the expense of REMS.

C5 Does the myelin and lymphocyte protein MAL play a functional role in intracellular Schwann cell signalling?

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The myelin and lymphocyte protein MAL is a raft-associated membrane protein in myelin membranes, predominantly expressed by Schwann cells. As MAL expression in the PNS starts already before myelination, we investigated its function during early postnatal development. Our results show that mice overexpressing MAL manifest a delayed onset of myelination, reflecting that MAL might play a key role in PNS myelinogenesis. Previous studies revealed a reduced expression of the neurotrophin receptor p75 (p75NTR), an essential receptor for initiating myelination, in sciatic nerves of newborn MAL-overexpressing mice (Buser et al, 2009). To define whether there is a direct link between the overexpression of MAL and the decreased expression of p75NTR, we started to establish different in vitro strategies. In primary mouse Schwann cell cultures, we have established stimulation assays with forskolin to mimic the axonal signal. By qRT-PCR, the degree of stimulation was measured by determining the expression of P0 mRNA, referred as a marker for stimulated Schwann cells. We could show that in cultures of MAL-overexpressing Schwann cells, P0 mRNA is decreased in both unstimulated and stimulated conditions, reflecting the observed phenotype in vivo. However, the degree of stimulation was comparable between MAL-overexpressing and wt cultures, suggesting that the signalling pathway of forskolin seems not to be affected by the overexpression of MAL. In addition, we could show a decreased level of p75NTR mRNA in transgene Schwann cell cultures, leading to the suggestion that there is a link between elevated MAL and decreased p75NTR expression even in vitro. In further studies, different stimulation agents like neuregulin and neurotrophins will be investigated to determine their effect on MAL-overexpressing cultures. To further investigate the potential link between MAL and p75NTR expression, we established proliferating rat Schwann cell cultures that are infected with a retroviral construct overexpressing MAL. By qRT-PCR, quantitative Western blot analysis and immunofluorescence stainings the expression level of p75NTR are currently determined, verifying whether the overexpression of MAL alone is sufficient to alter p75NTR expression or whether the observed reduced expression of p75NTR in vivo is a consequence of a cascade of events induced by MAL-overexpression. The aim of our studies is to elucidate whether MAL plays a direct role in axon-glia signaling for myelination.

C6 The functional role of the raft proteins MAL and PMP22 in the initiation of peripheral myelination

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The myelin and lymphocyte protein MAL is a raft-associated membrane protein playing a role in early Schwann cell development. MAL is expressed in Schwann cells before the onset of myelination and is involved in the stabilization of particular membrane domains. MAL-overexpressing mice (tgMAL) show a delay of membrane ensheathing, which was not longer present at one month of age (Buser et al., 2009). Some of the alterations observed in the tgMAL mice resemble those observed in mice overexpressing PMP22 (C22 line, Huxley et al., 1996). Like MAL, PMP22 is a tetraspan protein and a structural component of compact peripheral myelin; delayed myelination and hypomyelinated fibers are the common morphological alterations seen in C22 mice. In order to identify if MAL and PMP22 act via the same mechanism, or if they interfere with the myelination program via distinct mechanisms, we crossed these two mouse lines. Structural observations after birth show that myelination is not yet initiated in the tgMAL/C22 mice, whereas in wildtype mice a large number of axons are already myelinated. At postnatal day 10 the tgMAL/C22 mice show an almost absence of myelinated fibers, whereas in C22 mice 50% of the axons were already myelinated. At two month of age, when all myelinating fibers normally are established, the total number of myelinated fiber in the tgMAL/C22 mice is 60% lower. Although the segregated axons show a correct 1:1 relationship with the Schwann cell, enwrapping of the axon and compaction are strongly retarded in the double transgenic mice. Molecular analyses indicate that Schwann cell differentiation is not impaired, since they can express the known markers of myelination. These data suggest that overexpression of both MAL and PMP22 leads to a more than cumulative effect on myelinogenesis. Further studies are needed to describe the mechanisms by which the onset of myelination is stalled for almost two week.

C7 GABAB receptors are targeted to proteasomal degradation via interaction with the AAA-ATPase SUG-1

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Metabotropic GABAB receptors mediate slow inhibition in the CNS. Cell surface expression of GABAB receptors and thereby signaling strength is critically dependent on the rate of receptor degradation. Here we tested the hypothesis that the proteasome may contribute to the degradation of GABAB receptors. Blocking or enhancing proteasome activity resulted in increased and decreased levels, respectively, of GABAB receptors in cultured cortical neurons as tested using the "In Cell Western" assay. Moreover, we identified SUG-1, one of the six AAA-ATPases of the 19S regulatory complex of the proteasome, to interact with the C-terminal domain of GABAB2. Overexpression of SUG-1 in HEK 293 cells resulted in strongly reduced levels of co-expressed GABAB2, but did not affect levels of co-expressed GABAB1, confirming that SUG-1 specifically interacts with GABAB2. Deletion of the C-terminal domain of GABAB2 prevented the downregulation of GABAB2 in the presence of SUG-1. The GABAB2-SUG-1 interaction was further confirmed by analyzing their colocalization in cortical neurons using confocal microscopy. Blocking proteasomal activity resulted in considerably enhanced co-localization of GABAB receptors with SUG-1. Moreover, enhancing neuronal activity by activating glutamate receptors induced an increased co-localization of GABAB receptors and SUG-1. These findings indicate that GABAB receptors are targeted by interaction with SUG-1 to proteasomes for degradation.

C8 Paracrine factors secreted by Endothelial Progenitor Cells support viability of neuronal cells

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Background: Current evidence suggests that endothelial progenitor cells (EPC) exert regenerative functions in a variety of tissues by means of paracrine factors. In the present study we tested the hypothesis that soluble factors secreted by cultured EPC may also support neuronal cell functions and survival. Methodology: EPC were isolated from peripheral blood of healthy human donors by gradient centrifugation. Cells were cultured in hypoxic conditions (1.5% O₂) for 3 days to enhance the secretion of growth factors. Presence of growth factors in EPC-CM was screened by an antibody array. Primary rat ganglionic eminence (GE) from E14 rats and a human neural stem cell line derived from the ventral mesencephalic region of the developing human brain (ReNcell VM) were treated with EPC-CM for one week. Cell viability was then assessed by means of MTT assay. Results: The antibody array disclosed the presence of several neurotrophins and growth factors with broad cytoprotective activities in EPC-CM. Both GE and ReN VM cells exhibited increased viability when cultured in presence of EPC-CM compared to control medium. Conclusions: EPC might play a role also in brain tissue repair through remarkable paracrine actions. Our findings suggest that EPC-CM could have neuro-protective and neuro-regenerative properties. A deeper characterization of multifaceted EPC-CM constituents and their actions might lead to the development of cell free therapeutic interventions.

C9 HIF-1 stabilization supports cultured dopaminergic neurons

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Background. Oxygen plays a pivotal role in regulating cell functions in health and disease. Actual tissue oxygen levels in both the developing and adult brain measures about 2-3% only and a low oxygen tension is an important modulator of the neural stem cell niche. The responses to oxygen fluctuation are orchestrated by Hypoxia-inducible factor-1 (HIF-1). Notably, HIF-1 alpha activation and signaling triggers cytoprotection in many cell types including neurons. **Purpose.** Aim of the present study was to investigate the effect of HIF-1 alpha activation by chemical stabilization on survival of cultured dopaminergic neurons. **Methods.** Ventral mesencephali (VM) were isolated from Wistar rat fetuses (at embryonic day 14) and grown as organotypic free-floating roller tube (FFRT) cultures for one week. HIF activation was induced by DMOG [1mM] starting at day in vitro 2 until the end of the culture period. Tissue was then fixed and sectioned; untreated cultures served as controls. Sections were immunohistochemically stained for the dopaminergic cell marker tyrosine hydroxylase (TH) and for the cell proliferation-associated protein Ki-67. **Results.** Chronic DMOG treatment resulted in a significant increase of TH positive cells (by 50%) as compared to controls. Likewise, the number of Ki-67 positive cells in VM FFRT cultures was significantly augmented in the DMOG treated groups (by 70%) as compared to controls. **Conclusion.** Our findings suggest that stabilization of HIF-1 alpha provides a means to promote differentiation and / or survival of dopaminergic neurons. Moreover, the increased proliferation rate implies that a pool of precursor cells were stimulated by HIF-1 alpha stabilization. These data support previous reports assessing the possible therapeutic utility of HIF-1 alpha induction for Parkinson disease.

D. Molecular and Cellular Mechanisms: Learning and Memory

D1 Circuit Mechanism of Fear Memory Formation in Auditory Cortex

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Memory formation is one of the most fundamental and fascinating functions of our brain. While synaptic plasticity as the putative cellular mechanism of learning has been studied in great detail, we know much less about the interactions of different types of neurons in the local network leading to memory formation. To study this question, we record activity in identified neurons in auditory cortex during formation of an associative auditory fear memory. We have developed a fear conditioning protocol employing frequency-modulated sweeps as conditioned stimuli. Acute inactivation of auditory cortex by infusion of the GABAA agonist muscimol during conditioning impairs learning, suggesting that auditory cortex is required for memory formation in this paradigm. In vivo 2-photon targeted patch-clamp recordings in anaesthetized mice show that foot-shocks cause strong activation of certain classes of inhibitory interneurons. In contrast, other interneuron classes are inhibited during foot-shocks, which ultimately leads to a dis-inhibition of layer 2/3 pyramidal neurons. In agreement with this finding, 2-photon calcium imaging experiments indicate that acute pairing of a tone with a foot-shock enhances the network response to the tone in neocortical layer 2/3. Finally, blocking the observed dis-inhibition during fear conditioning of awake behaving mice by optogenetic means severely reduces memory formation. Together, these results suggest that auditory cortex is required for fear learning under certain conditions. Moreover, we find that foot-shocks acutely affect the activity of several identified interneuron classes in neocortex, and that the resulting dis-inhibition is required for memory formation.

D2 Notch1 ablation induces molecular changes in plasticity genes that contribute to memory formation.

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Beside the essential role of Notch in development, this signaling pathway has been involved in neuronal morphology, synaptic plasticity, learning and memory. We have recently shown that Notch and its cognate ligand Jag-1 are expressed at the post and pre-synaptic terminal, respectively. In addition, Notch signaling is induced, in neurons, upon sensory experience through the facilitation of the early immediate gene *Arc/Arg3.1*. Targeted loss of function of Notch in the mature hippocampus has confirmed that this pathway is required for synaptic plasticity and novel memory acquisition. The mechanism beyond Notch function remains to be fully elucidated. Here we present several lines of evidence of the profound changes at the level Glutamate receptor and secondary messengers that occur in absence of Notch1. Notch1cKO hippocampi show a strong decrease in NMDARs as well as GluRs. As a consequence of reduced NMDAR's levels, we observe a decrease in CamKII expression, which is known to modulate NMDAR dependent plasticity. At the level of secondary messengers, that mediate the molecular changes associated with memory formation, we show that phosphorylation of ERK is reduced, and that the total levels of CREB are also decreased. In Notch1cKO aging mice we observe a profound loss of dendritic spines without any major effect on the dendrites' length, on the other hand the dendrites are characterized by abundant varicosities, indicative of neurodegeneration. These findings suggest that, in the Notch1cKO mice, the molecular players of memory are profoundly altered, and that in older mice signs of degeneration are present. At this point we do not know whether this is a direct or indirect consequence of Notch ablation, but this report underlines the important role of Notch in synaptic plasticity and highlights the relevance of this cellular cascade in Alzheimer's or Down's syndrome where the cognitive and morphological impairment have been reported in association with Notch dysfunction.

D3 RSK2 affects neuronal development and synaptic activity through PLD1

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Coffin-Lowry syndrome (CLS) is a syndromic form of X-linked mental retardation, which is characterized in male patients by psychomotor and growth retardation and various skeletal anomalies. CLS is caused by mutations in the RPS6KA3 gene located at Xp22.2, which encodes RSK2, a growth-factor-regulated protein kinase. RPS6KA3 mutations are extremely heterogeneous and lead to loss of phosphotransferase activity in the RSK2 kinase, most often due to premature termination of translation. Cognitive deficiencies in CLS patients are prominent, but markedly variable in severity, including between siblings. The pathophysiology of CLS is incompletely understood, but some data suggest that this syndrome may be caused by abnormalities in neural development and neurotransmission. In chromaffin cells, RSK2 regulates catecholamine release through the phosphorylation of PLD1 at Thr147. PLD1 has been proposed to be involved in neurite outgrowth in neurons and PC12 cells. In order to clarify how the loss of RSK2 activity causes CLS, we try to characterize and determine the relationship between RSK2 and PLD1 in neurite outgrowth and neurotransmission. Our primary results showed that Rsk2-KO neurons in culture have a delay of development. Using PC12 cell culture and specific PLD inhibitors, we confirmed that PLD is involved in neurite outgrowth, especially in the first stage of development. Finally electrophysiological results show that RSK2 seems to be engaged in presynaptic compartment and that RSK2 regulates the exocytosis/endocytosis machinery.

D4 Genome-wide profile of H4K5 acetylation for fear memory-regulated genes

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Learning and memory are cognitive processes requiring molecular and genetic transformations in the brain, however, epigenetic modifications to the genome has also been proposed to be involved. One of the mechanisms to modify chromatin state is histone posttranslational modifications (PTMs). Although the identities and functions of histone PTMs have not been fully characterized, histone acetylation, in general, has been associated with active gene transcription. To determine the role of chromatin remodeling-regulated gene expression in memory, we turned to genome-wide analysis of histone H4K5 acetylation (H4K5ac). Using chromatin-immunoprecipitation followed by massively parallel sequencing (ChIP-Seq), we identified 23,235 genes in which absolute expression correlated to enrichment for H4K5ac. We found that the highest expressed genes concomitantly had the highest enrichment for H4K5ac at both the promoter and coding regions but not at the TSS, even when genes were clustered, in silico, based on their acetylation profile. Expressed genes, however, had less acetylation at promoter positions that had a transcription factor binding site present suggesting they are mutually exclusive events. Using H4K5ac as a marker, a modification known to be induced after fear-conditioning in mice, we were also able to identify, de novo, genes known to be involved in memory consolidation and genes previously unidentified in memory processes. We have also identified novel microRNAs that may serve to regulate memory-specific genes. Together, our data suggests that histone acetylation, particularly on H4K5, is a PTM necessary not only for active gene transcription, in general, but is also a key determinant of genes induced by fear learning.

E. Neural Excitability Synapses: Functional Aspects

E1 High-efficiency Channelrhodopsins for fast neuronal stimulation at low light levels

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Channelrhodopsin-2 (ChR2) has become an indispensable tool in neuroscience, allowing precise induction of action potentials with short light pulses. A limiting factor for many optophysiological experiments is the relatively small photocurrent induced by ChR2. We screened a large number of ChR2 point mutants and discovered a dramatic increase in photocurrent amplitude after threonine-to-cysteine substitution at position 159. When we tested the T159C mutant in hippocampal pyramidal neurons, action potentials could be induced at very low light intensities, where currently available channelrhodopsins were unable to drive spiking. Biophysical characterization revealed that the kinetics of most ChR2 variants slows down considerably at depolarized membrane potentials. We show that the recently published E123T substitution abolishes this voltage sensitivity and speeds up channel kinetics. When we combined T159C with E123T, the resulting double mutant delivered fast photocurrents with large amplitudes and increased the precision of single action potential induction over a broad range of frequencies, suggesting it as a new standard for light-controlled activation of neurons.

E2 Modulation of the GABAergic system in the basolateral complex of the amygdala: Action of the anxiolytic drug Etifoxin

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The amygdala is a major control center of the emotions, but also integrates sensory, especially nociceptive information. The descending nociceptive pathways located in the hindbrain are modulated by amygdala efferences. It has also been clearly established that inhibitory post-synaptic currents (IPSPs) in projection neurons of the basolateral complex of the amygdala (BLA) are essential in the processes of negative emotional responses, as well as for pain expression. GABAA Receptors present on BLA neurons possess subunits that are sensitive to anxiolytic molecules, like benzodiazepines. Previously, it has been shown that Diazepam increases the spontaneous and miniature IPSCs amplitude and tau decay in BLA neurons. In this study, we focus on the effect of a non-benzodiazepinic anxiolytic drug Etifoxin (EFX). This molecule acts as a positive modulator of the GABAA Receptor, by binding directly on the receptor and by increasing the synthesis of neurosteroids, also known as strong modulator of GABAA receptor.

We use coronal amygdala slices, obtained from C57BL/6J mice, 21-28 days old. Using a patch-clamp approach, in the whole-cell configuration, we record the synaptic inhibitory transmission. Patch-clamp recording of the miniatures IPSCs (mIPSCs) of BLA neurons shows that EFX potentiates inhibition via 3 different mechanisms. Neurons can present an increase of the amplitude of their mIPSCs, or of the frequency of them, or of the tau decay of their mIPSCs or of a combination of these 3 effects. To discriminate between the direct and the indirect effect of EFX, we plan to specifically block neurosteroids synthesis. Thus we will be able to only observe the direct EFX effect on the GABAA Receptors.

F. Brain Metabolism and Homeostasis

F1 Regulation of cortical interneuron function by metabolic substrates

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Astrocytes are described to deliver the metabolic substrate lactate to neurons in response to glutamatergic activity. It remains to be determined if this mechanism applies to GABAergic interneurons, inasmuch as GABA uptake in astrocytes does not evoke a metabolic response. The aims of this study are to determine whether interneurons send a metabolic signal to astrocytes, and whether energy equivalents delivered by astrocytes could sustain or influence interneuron activity. Primary cultures of cortical neurons were obtained from E17 C57BL/6 and GAD67-GFP knock-in mice, and used at DIV 12-20. Immunohistochemistry indicated a proportion of 10% of GABAergic interneurons in the cell cultures, compatible with that found in situ in the rodent cerebral cortex. Neuron excitability was monitored by electrophysiological recordings and calcium imaging using the fluorescent probe Fluo-4 AM. Spontaneous action potentials and rhythmic calcium spikes were present in more than 50% of cultured neurons, both GABAergic and glutamatergic. In the presence of 5mM glucose, L-lactate application diminished calcium transient frequency in a concentration-dependent manner in both cell types (glutamatergic neurons IC₅₀ 4.23±1.9mM and GABAergic neurons IC₅₀ 4.18±2.8mM). The activity was restored after lactate washout. The stereoisomer D-lactate and pyruvate both decreased calcium transient frequency in the same concentration range. In contrast, switching to 0.5 or 10mM glucose did not alter calcium transient frequency. Because lactate was described not to influence synaptic release, our observed sensitivity to lactate suggests the involvement of intrinsic or network mechanisms. This modulating effect of lactate is to be taken into account in the context of neurometabolic coupling.

F2 Sensory stimulation alters the expression of cardiac troponin C, PACAP, and NPAS4 in the adult mouse barrel cortex

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Sensory informations are integrated and constantly updated by our brain to properly interact with the ever-changing environment. The ability of the nervous system to change in response to experience relies on the plastic properties of the neuronal network. Layer IV of the barrel cortex of the mouse consists of excitatory and inhibitory interneurons that, together with the astrocytes, react onto increased sensory stimulation in a very robust manner. Cells from this layer are capable to respond to an increased level of neuronal activity to maintain a level of homeostasis turning the barrel cortex into a model to study homeostatic plasticity.

To further characterize the molecular pathways involved in the synaptic modifications after whisker stimulation, preliminary micro-array analysis were performed on laser-dissected barrels in sections through layer IV and revealed an upregulation of a series of genes in the stimulated barrels. Starting from these results, we focused on the three following genes according to their implication in synaptic plasticity:

- 1) cardiac Troponin C, a calcium binding protein and a structural constituent of the cytoskeleton, is induced in the visual cortex during the critical period (Lyckman et al., 2008)
- 2) NPAS4 is a transcription factor implicated in the development of GABAergic synapses development and regulated by neuronal activity (Lin et al., 2008)
- 3) Pituitary Adenylate Cyclase Activating Polypeptide (PACAP), a neuropeptide involved in many intracellular cascades such as the long-term synaptic plasticity (Botia et al., 2007) is implicated in the regulation of two synaptic plasticity related-molecules: the NMDA receptors and the BDNF protein (Yaka et al., 2003).

In the present study, we aim to validate the mRNA results for these three genes using in situ hybridization and to further determine for each gene, the protein expression pattern with immunohistochemistry.

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-Lyckman et al., PNAS 105 : 9409-9414 (2008) -Yaka et al., Journal of biological chemistry 278: 9630-9638 (2003)

F3 The RNA-binding protein RBM3 is involved in hypothermia induced neuroprotection

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Induced hypothermia is the only therapy with proven efficacy to reduce brain damage after perinatal asphyxia. While hypothermia down-regulates global protein synthesis and cell metabolism, low temperature induces a small subset of proteins that includes the RNA-binding protein RBM3 (RNA-binding motif protein 3), which has recently been implicated in cell survival. Here, immunohistochemistry of the developing postnatal murine brain revealed a spatio-temporal neuronal RBM3 expression pattern very similar to that of doublecortin, a marker of neuronal precursor cells. Mild hypothermia (32°C) profoundly promoted RBM3 expression and rescued neuronal cells from forced apoptosis in PC12 cells and cortical organotypic slice cultures. Blocking RBM3 expression in neuronal cells by specific siRNAs significantly diminished the neuroprotective effect of hypothermia. Together, neuronal RBM3 up-regulation in response to hypothermia apparently accounts for a substantial proportion of hypothermia-induced neuroprotection.

F4 Cerebral metabolic compartmentation determined by high resolution in vivo ¹³C NMR spectroscopy

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The combination of dynamic ¹³C nuclear magnetic resonance (NMR) spectroscopy with the infusion of ¹³C-enriched substrates is a powerful method to probe metabolic fluxes in vivo. With this work we aimed to study brain metabolism with higher sensitivity and spectral resolution provided by the increased magnetic field at 14.1T. Male Sprague-Dawley rats under chloralose anaesthesia were infused with [1,6-¹³C]glucose, while ¹³C spectra were measured. Localized ¹H and ¹³C NMR spectroscopy was performed on a 14.1 T, 26 cm VNMR spectrometer (Varian, Magnex) with a coil consisting of a ¹H quadrature surface coil and a ¹³C linearly polarized surface coil. ¹³C NMR spectra were acquired using semi-adiabatic distortionless enhancement by polarization transfer (DEPT) combined with ¹H localization and were quantified with LCModel. Excellent sensitivity was evident from the measured ¹³C spectra. High spectral resolution allowed complete separation of C2 and C3 resonances of glutamate and glutamine, which was not possible at lower fields, as well as good observation of their multiplets resulting from homonuclear coupling in multiply labelled metabolites. Fractional enrichment in aliphatic carbons of glutamate and glutamine were determined in 5 animals with high reproducibility, thus increasing accuracy in determination of cerebral metabolic fluxes with appropriate mathematical models. Multiplets were clearly observed and isotopomer analysis could be performed in vivo for different metabolites, including glutamate, glutamine, aspartate and GABA. Fractional enrichment of glutamate and glutamine carbons was accurately determined with 3 minutes of time resolution. At lower temporal resolution there was reliable determination of labelling incorporation into carbons of metabolites with slow synthesis rate or occurring at lower concentration, like aspartate and GABA (12 minutes) or glutathione and N-acetylaspartate (30 minutes). Mathematical modelling with two cerebral metabolic compartments allowed reliable determination of metabolic fluxes including VTCA of 0.44±0.01 mmol/kg/min and 0.22±0.01 mmol/kg/min in neurons and glia respectively, and a neurotransmission flux VNT of 0.14±0.01 mmol/kg/min. Direct detection of ¹³C enrichment of cerebral metabolites with DEPT was improved at 14.1 T with gain in sensitivity and especially in spectral resolution. Upon infusion of [1,6-¹³C]glucose, numerous ¹³C-enriched metabolites could be quantified over the entire time course. In addition, LCModel allowed maximizing the amount of information that can be extracted from ¹³C spectra. All this together may increment the reliability of complex mathematical models describing cerebral energy metabolism. This work was supported by Centre d'Imagerie BioMédicale (CIBM) of the UNIL, UNIGE, HUG, CHUV, EPFL and the Leenaards and Jeantet Foundations; and by SNF grant 131087.

G. Cognitive and Behavioral Neuroscience

G1 Development of a screening device for assessing visual attention in occupational health practice

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Visual attention is of crucial importance in many tasks at work, like in driving or in surveillance. Occupational health has gained practical evidence about significance of visual attention for safety at work, as inattention has been ruled out as factor in accidents or as cause lowering quality of work and productivity. Efficient improvement of conditions at work, requires an objective and ecological valid quantification of visual attention performance. We develop a simple to use device for rapidly screening visual attention performance in occupational health practice. The method consists in presenting tachistoscopically (300 ms) 6 digit numbers at a random position and at a random time, which are overlaid on a background representing a movie of a car drive. Participants are asked to detect the digit "3" in presented numbers. Data are analyzed by means of signal detection theory. Subject's health status is assessed by means of a questionnaire. Since the project aims to record reference data for the normal, healthy population, data of subjects with pathologies and medications (self declaration) are separated from data of healthy subjects. Up to date, a total of 127 (78 m, 49 f) with an age ranging between 16-80 y took the test. An additional 40 data sets will be available in February 2011. From data, percentile values for detectability (d') and reaction time are computed for various ranges of age. As expected, detectability in the central visual field is higher than in periphery. For the periphery, we found a significant difference in detectability between healthy subjects and subjects with pathologies or with medications (although the solely aim of this project is to set-up standards for a healthy population). The device has proven good acceptance in practice of occupational health.

G2 Insulin resistance, hypertension and Attention Deficit Hyperactive Disorder: is there a link?

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The spontaneous hypertensive rat (SHR) shares many of the behavioural characteristics of humans diagnosed with Attention Deficit Hyperactivity Disorder (ADHD) and is used commonly as an animal model to address the neurobiological endophenotypes that may be related to this condition. The aim of this study was to find a link between metabolic syndrome (as insulin resistance), hypertension and ADHD. We investigated 3 and 7 months old SHR and measured learning behavior, insulin receptor (IR)- β subunit (total/ phosphorylated) and glycogensynthase-kinase-3 (GSK3)- β subunit (total/ phosphorylated) levels in different brain regions, glucose intolerance and blood plasma insulin level. Using passive avoidance and Morris water maze tests, all SHR showed significantly worse learning success compared to the control animals. In all brain regions (frontal cortex, hippocampus and striatum) IR β level was significantly decreased in 3 and 7 month old SHRs but phosphorylated IR β amount was increased. We could also find significant decreased level of GSK3 β in 3 month old SHR in all investigated brain regions but non significant changes in phosphorylated GSK3 β . In 7 months old SHRs we detected significant increased level of phosphorylated GSK3 β in frontal cortex and hippocampus. Testing glucose intolerance showed no significant changes between SHR and their controls, but plasma insulin level was significant increased in all investigated SHRs. In summary, we could show significant alterations in IR β , GSK3 β brain amount and blood insulin level in 3 & 7 months old SH rats compared to their control, which indicates a possible link between insulin signalling pathway and hypertension with ADHD.

G3 Spontaneous brain activity engenders perception and determines discrimination sensitivity

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Extant evidence documents that behavioral and brain responses to identical stimuli vary as a function of the context of stimulus presentation, task instructions or even spontaneous modulations of attention. However, computational models suggest that spontaneous fluctuations in brain activity could be sufficient to engender perceptual differences such that on a given percentage of trials, physically identical stimuli are (mis)perceived as differing. Here, we tested whether and how variations in brain responses to identical stimuli can yield perception by applying electrical neuroimaging analyses to auditory evoked potentials (AEPs) recorded from healthy humans as they indicated which sound of a pair of identical pure tones was perceived as higher in pitch. Topographic modulations were observed over the 93-115 post-stimulus interval, indicative of distinct configurations of active brain networks. Distributed linear source estimations revealed significantly stronger activation within left temporo-parietal areas for stimuli perceived as lower pitch vs. higher -pitch. Importantly, activity within this cluster for both perceived pitch conditions negatively correlated with the participant's sensitivity in pitch discrimination measured prior to the experiment, confirming that the brain's level of spontaneous variability is linked to perceptual proficiency. We discuss our results in terms of providing neurophysiologic evidence for the contribution of internal noise to conscious perception, discrimination abilities and in explaining improvements in pitch discrimination thresholds following training with acoustically identical sounds.

G4 Discrete stages in the development of hippocampus-dependent spatial memory in children.

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Episodic memories for events that happen in unique spatiotemporal contexts are central to defining who we are. Yet, there is a significant period during early childhood when episodic memories are incapable of being formed or recalled. Here, we studied the development of spatial relational memory, a fundamental component of episodic memory, which is dependent on the integrity of the hippocampus in adult subjects. Children were tested in a real-world spatial memory task. Rewards were hidden beneath cups distributed in an arena, in presence or absence of local cues marking the rewarded locations. One group of children was tested with one rewarded location amongst four potential locations, whereas another group of children was tested with three rewarded locations amongst 18 potential locations. In the group of children aged 18-47 months (n=35) tested with four potential locations, 61% of 18-23-month-olds found the rewarded location reliably in the presence of the local cue, whereas 100% of the 24-47-month-olds did. In the spatial relational condition (no local cue), only 22% of the 18-23-month-olds tested found the rewarded location reliably, whereas 88% of the 24-47-month-olds did. In the group of children aged 23-61 months (n=44) tested with 18 potential locations, all children found the three rewarded locations reliably in the presence of the local cues. In contrast, in the spatial relational condition (no local cues), only 18% of the 23-41-month-olds found the rewarded locations reliably, whereas 96% of the 44-61-month-old children did. These findings indicate that the ability to form a basic allocentric representation of the environment is already present in 24-month-old children. However, more precise, potentially richer, spatial relational memories develop between 24 and 44 months of age. These discrete developmental stages might be dependent on the maturation of specific hippocampal circuits, which in turn may underlie the eventual emergence of episodic memory.

G5 The right dorsolateral prefrontal cortex prevents post-error slowing

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Adjusting behavior following the detection of inappropriate actions allows flexible adaptation to task demands and environmental contingencies during goal-directed behaviors. Post-error behavioral adjustments typically consist in adopting more cautious response mode, which manifests as a slowing down of response speed. Although converging evidence involve the dorsolateral prefrontal cortex (DLPFC) in post-error behavioral adjustment, whether and when the left or right DLPFC is critical for post-error slowing (PES), as well as the underlying brain mechanisms, remain highly debated. To resolve these issues, we used single-pulse transcranial magnetic stimulation to disrupt the left or right DLPFC selectively at various delays within the 30-180ms interval following false alarms commission, while participants performed a standard visual Go/NoGo task. PES significantly increased after TMS disruption of the right, but not the left DLPFC at 150ms post-FA response. We discuss these results in terms of an involvement of the right DLPFC in reducing the detrimental effects of error detection on subsequent behavioral performance, as opposed to implementing adaptative error-induced leftward shifts of the speed-accuracy tradeoff.

G6 Right DLPFC and VMPFC orchestrate normative decision-making

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Humans are unique in their capacity to override self-interest in favor of normatively valued goals. Despite progress in recent years little is yet known about the neural underpinnings of this capacity. Here we examine the neural circuitry causally involved in normative, fairness-related decisions of responders in the ultimatum game. We generate a temporarily diminished capacity for costly normative behavior – a “deviant” case – through noninvasive brain stimulation (rTMS), and compare “normal” subjects’ fMRI signals with those of the “deviant” subjects. When fairness and economic self-interest are in conflict, “normal” subjects – who make costly normative decisions at a much higher frequency – display significantly higher activity in, and connectivity between, the right dorsolateral prefrontal cortex (DLPFC) and the posterior ventromedial prefrontal cortex (pVMPFC). In contrast, when there is no conflict between fairness and economic self-interest, both types of subjects display identical connectivity patterns and behave identically. “Normal” and “deviant” subjects also show no differential activation in any other brain region during the processing of unfair offers, suggesting that a parsimonious prefrontal network – the activation of right DLPFC and pVMPFC, and the connectivity between them – facilitates subjects’ willingness to incur the cost of normative decisions. These findings impose important constraints on neural models of normative choice and suggest common neural foundations for the valuation of goals in normative and non-normative domains.

G7 Neural correlates of birdsong variability in different social contexts

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Male Zebra finches use learned vocalizations to court females (directed song). They also sing for themselves (undirected song). Both song types differ in various aspects but are generated by the same two major neural pathways. The first pathway, located in the posterior part of the brain, is necessary and sufficient for song production. The second pathway, located in the anterior part of the brain, is necessary for song learning, moment-by-moment variability, and vocal plasticity. The output nucleus of the anterior pathway is LMAN. LMAN projects to nucleus RA, the point of convergence of the song production and learning pathways. We performed extracellular recordings of single RA-projecting LMAN neurons in freely behaving and singing male zebra finches. We recorded from neurons in directed and undirected conditions. Preliminary data suggests a negative correlation between motif durations and single unit firing rates. Further, we observed fine-grained changes in the song structure that appear to be correlated both with the motif duration and LMAN firing. Our work provides new insights into neural mechanisms of learned social behaviours.

G8 The role of single-trial, episodic multisensory learning in unisensory object discrimination

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Single-trial multisensory experiences can influence the ability to accurately discriminate image repetitions during a continuous recognition task. Pairing visual objects with their corresponding sounds can enhance subsequent visual discrimination, whereas pairing visual objects with an identical pure tone has been shown to impair subsequent visual discrimination compared with performance with objects only encountered visually. Despite their opposing polarity, these effects indicate incoming visual stimuli access multisensory memory traces established through single-trial learning. One open issue is the role of semantic versus episodic multisensory experiences, because prior work was confounded by pairing different visual objects with an identical pure tone. Here, we determined the role of episodic multisensory experiences by pairing (on their initial encounters) visual objects with meaningless, but unique sounds. Subjects discriminated initial from repeated presentations of images of common objects. Half of the initial presentations of images were presented in a unisensory visual manner. Each of the remaining half of the images was paired on its initial presentation with a distinct but meaningless sound in a multisensory context. All repeated presentations were exclusively unisensory visual. Accuracy in recognition of repeated images was impaired for those that had been initially presented in a multisensory context. This decrement was dissociable from performance during initial image presentations, ruling out explanations in terms of attention or direct transfer from encoding to retrieval. Instead, the results indicate that the direction of the impact of single-trial multisensory memories on visual object discrimination is linked to the semantic versus episodic contingencies between the senses.

G9 Impact of emotion, sleep and re-test on face-name association learning.

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In this study, we investigated whether emotion facilitates the learning of face-name associations by comparing smiling and neutral faces. The impact of sleep was tested by varying the time of testing (i.e. morning = long interval between learning and sleep, versus evening = short interval). Finally, the role of repeated testing in enhancing memory was assessed by comparing performance on several retrieval tests separated by 12 hours. Sixteen healthy controls learned face-name associations using a paradigm of errorless learning with pre-exposure of the face. Each participant learned 40 face-name associations divided into two lists of 20 associations and was asked to recall the name associated with each face following a 2-minute interval filled with a distractive task. One week later, participants came back for 3 retrieval assessments separated by 12 hours. The 40 learned faces were presented one at a time and participants had to recall each associated name. In case of failure, the correct answer was not given. Our results showed a ceiling effect at the 2-minute-delay post-test and no effect of emotion. After one week, performance had significantly declined; emotion had again no significant effect. More importantly, repeated testing at one week lead to better name recall across the three retrieval tests with the third one being significantly superior to the first one. Interestingly, this was observed independently of the interval between learning and sleep, as it occurred for both groups (8 am and 8 pm). Possible explanations for the absence of memory enhancement by emotion will be considered. The positive effect of repeated testing will be discussed in reference to concepts such as reconsolidation and accessibility.

G10 Dissociation between frontal and parietal lesion in spatial neglect patient

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Spatial neglect is a perplexing neuropsychological syndrome, in which patients fail to detect contralesional stimuli. A recent study showed that spatial neglect may reflect a combination of different component deficits, two of which were associated with lesions in the right prefrontal and inferior parietal regions, respectively. The present study tested for dissociable behaviors across two tasks designed to probe for such components in 14 patients with right frontal versus parietal damage, respectively. In the "attention control" task, patients had to respond to visual stimuli presented centrally in three conditions. Only the frontal patients showed slower reaction times when central stimuli were presented with a right distractor. In the "spatial remapping" task, patients were asked to detect a target in a series of successive visual stimuli presented horizontally across three conditions. The parietal patients were unable to benefit from the predictability of the target position, with similar reaction times across all conditions; by contrast, patients with frontal lesions showed progressive decreases in reaction times in conditions with a regular succession of stimuli (compared to the random condition). Taken together, these results support the view that frontal damage may contribute to left inattention by disrupting top-down control and resistance to distractors, while parietal damage may disrupt the maintenance of stable locations in space across eye movements or time. This further suggests that left neglect may arise as a combined breakdown or impaired connectivity between frontal and parietal regions involved (respectively) in the executive and storage components of spatial working memory.

G11 Tracking the brain dynamics of gut hormone influences on food image discrimination in normal-weight women across hunger states

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Endocrine factors convey information about energy needs to brain regions involved in the homeostatic control of feeding. Likewise, both the control of food intake and viewing of foods (independent of their ingestion) also address brain areas implicated in reward evaluation and decision-making. The extent to which low-level endocrine factors interact with higher-level cognitive processes and brain areas involved therein is still unknown. We concurrently recorded endocrine factors and visual evoked potentials (VEPs) during food and non-food image viewing in women following an overnight fast and in post-prandial state. Global VEP differences as a function of nutrition state surfaced from 130ms post-image onset. In a hungry state, VEPs to foods vs. non-foods differed substantially earlier (~130ms) than in post-prandial state (~195ms). Neural source estimations identified differences between the responses to food and non-food stimuli in a wide network of brain regions typically associated with food object processing, food motivation and also decision-making. In particular, neural activity in regions showing reliably higher responses to food viewing was found to vary by nutrition state. The modulations in neural source activity during food viewing correlated negatively with insulin blood levels in fasted state, i.e. with a digestive hormone usually released only after food intake. On the other hand, positive correlations were observed with blood-level concentrations of ghrelin and the pancreatic peptide YY in post-prandial state, i.e. with hormones regulating food intake motivation. These findings reveal interactions of nutrition state and the gut-brain axis that are central to understanding deviant eating behaviors leading and for developing intervention strategies.

G12 Neural control of a motor pattern in zebrafish: an optogenetic analysis

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To study the relationship between neuronal activity in defined populations of neurons and behavioral output, we screened zebrafish larvae expressing channelrhodopsin-2 (Chr2) for changes in swimming behavior evoked by exposure to blue light. Here we present results from a stable line that moves backwards in response to blue light. Detailed video analysis revealed that tail and fin movements during channelrhodopsin evoked swimming closely resemble J-turns, a motor motif that occurs during prey capture and serves to adjust the position of the fish relative to its prey. J-turn-like fin and tail movements also occurred in response to blue light stimulation when the head of larvae was embedded in agarose, indicating that it is an intrinsic motor pattern. Mapping of behavioral responses to focal blue light stimulation revealed that J-turn-like swimming is triggered specifically by optical stimulation of the deep anterior midbrain or posterior diencephalon. We are currently combining focal optical stimulation with calcium imaging in a brain explant preparation and in vivo to study the distribution of neuronal activity associated with J-turn-like swimming. These results are beginning to unravel the higher-order neuronal circuitry controlling a defined motor behavior.

G14 Functional connectivity of the resting brain in obsessive compulsive disorder

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Spontaneous patterns of functional brain connectivity during resting are altered in neurological and psychiatric diseases. Here we studied how resting network connectivity differs between obsessive-compulsive disorder (OCD) patients and healthy controls, and how it is modulated by stress induction.

We acquired functional MRI (fMRI) data during a 'classical' resting state condition and when resting state was associated with stress induction. First we determined regions of interest (ROIs) using independent component analysis (ICA). We then used wavelet-based correlations to assess functional connectivity between these regions for slow and fast frequency ranges of fMRI signal. Bootstrapping statistics revealed distinct networks between groups (OCD vs controls) and conditions (resting state vs induction).

During resting state, OCD patients (vs controls) showed increased connectivity between striatum, ventro-medial prefrontal cortex (VMPFC), and insular regions, selectively for fast oscillations (0.14-0.28 Hz). By contrast, at slow oscillations (0.02-0.04 Hz), controls (vs patients) showed increased connectivity in the default-mode network.

Stress induction enhanced connectivity between the caudate, insula and ACC in OCD patients, while connectivity within a network encompassing VMPFC and nucleus accumbens was strengthened in the controls. These effects were found for fast oscillations of fMRI signal.

This pattern of results suggests that the pathophysiology of OCD may involve disturbances across multilayered neural networks oscillating at different frequencies that are related to motivation and the regulation of internal states (providing an increased emotional vulnerability to patients). Such disturbances were partially mimicked by a stress induction procedure in the controls, providing neural evidence for increased stress-eliciting thoughts in OCD.

G15 Upside Down: Visual-vestibular conflict induces illusory changes in the experienced direction of the first-person perspective

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Bodily self-consciousness has been hypothesized to rely on self-identification, self-location and the first-person perspective (Blanke, Metzinger, 2009). This has been demonstrated by manipulating self-identification and self-location with visual-tactile conflicts in different full-body illusions (Lenggenhager, 2007; 2009; Ehrsson, 2007). Multisensory mechanism of the first-person perspective (1pp) are less well understood (Blanke, 2008). Here we employed visuo-tactile and additional visual-vestibular conflicts to investigate 1pp by extending a real-time robotic setup. Visuo-tactile stimulation was presented on a virtual body (i.e. back view image of a body at extracorporeal location) and participant's own body in synchronous or asynchronous fashion (Stroking, within-subject factor). Virtual body orientation in space differed from participant's orientation in order to induce strong or weak visual-vestibular conflict (VVC, within-subject factor). Questionnaire ratings for 1pp-direction and self-identification with the virtual body were acquired as well as response times (RTs) for self-location (Lenggenhager, 2009). As expected based on pilot data, questionnaire analysis revealed two participant groups that differed for ratings of 1pp-direction (Down-Looker (N=9), Up-Looker (N=14)) (Group, between-subjects factor). Both groups showed higher scores for self-identification during synchronous as compared to asynchronous stroking. RT analysis revealed synchrony-related changes of experienced self-location that were modulated by 1pp-direction, RTs decreased with synchrony for Down-Lookers, but increased for Up-Lookers. Furthermore, only Down-Lookers modulated RTs with VVC. Together these results demonstrate inter-individual differences concerning visual-vestibular mechanisms in the 1pp and demonstrate that 1pp shares functional mechanisms with self-location, but not with self-identification.

G16 Dopaminergic modulation of learning about a person's trustworthiness

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In our daily life we need to know whom to trust or to distrust. We learn about a person's trustworthiness by getting positive and negative feedback while interacting with this person. Apparently, receiving positive returns from a partner is rewarding which is reflected by an increase in activity in the reward system, specifically in the striatum (Rilling et al., 2002). The extent of this activity in turn is predictive for future trusting behavior (King-Casas et al., 2005), suggesting that the striatum might encode a dopaminergic reward-processing signal, which influences learning about a person's trustworthiness.

While drug challenge studies have shown that administration of dopaminergic drugs may modulate striatal reward processing, recent studies also suggest a role of endogenous dopamine levels on striatal function. Variation in the dopamine transporter gene (DAT1 polymorphism), which is thought to affect baseline dopamine turnover in the striatum, has been demonstrated to influence reward-processing (Forbes et al., 2007, Aarts et al., 2010).

In summary, there is evidence that learning about a person's trustworthiness may be governed by striatal reward processing, which might be affected by endogenous, as well as exogenously manipulated, dopamine levels.

To establish a causal role for dopamine in learning about a person's trustworthiness, we administered 300 mg of L-DOPA, the biochemical precursor of dopamine, or a placebo to 205 healthy male subjects who played a repeated trust game in the role of the investor and genotyped them for their DAT1 VNTR polymorphism. Investors played several rounds with two different trustees, each associated with different tendencies to reciprocate cooperation, which were unknown to the investors at the beginning of the experiment.

Results show that L-DOPA influences the efficiency to learn about a person's trustworthiness depending on the variation of the DAT1 genotype. This finding indicates that the complex, yet vital mechanism of learning whom to trust is linked to the DA system. Furthermore, on a more general basis, we demonstrate that a pharmacogenetic approach may be promising for the understanding of multifaceted social behavior.

G17 Age dependent decrease of adult hippocampal neurogenesis in the wild South African Namaqua rock mouse is gender-specifically regulated

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The Namaqua rock mouse (*Micaelamys namaquensis*) is distributed throughout the southern African subregion. These nocturnal terrestrial mice prefer rocky, dry habitats and are exposed to strong seasonal changes. Similar to European wood mice, habitat use differs between females and males, the latter having larger territories overlapping the territories of several females. During summer seasons with high temperature (up to 45°C degrees), these mice undergo a "summer sleep" to conserve energy and water. Considering these interesting characteristics, we investigated adult hippocampal neurogenesis in these animals. Earlier studies have shown that adult hippocampal neurogenesis differs significantly among wild-living rodents. It is down regulated with age, but at different time points in life history. Also, it has been shown that a sex difference in neurogenesis during breeding and non-breeding seasons in meadow voles is associated with hormonal changes and use of variable territory sizes. For the study presented here, we trapped Namaqua rock mice in the Limpopo region of South Africa at the beginning of spring and analysed the hippocampus for immunohistochemically stained young neurons (Doublecortin). Quantification followed the rules of design-based stereology (optical fractionator). As an indicator of age, we used the weight of the eye lenses. A first analysis shows a significant age dependent decrease of the number of Doublecortin-positive cells. Furthermore, a significant difference between females and males becomes apparent. These results confirm earlier findings of decreased adult hippocampal neurogenesis in wild rodents with age. The sex difference in neurogenesis might be related to the fact that males and females differ in (space use) behaviour and hormonal status, as the animals were caught at the beginning of the breeding season.

G18 Physiological correlates of subjective time: evidence for the temporal accumulator hypothesis

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Clock-counter models, the most influential cognitive models of temporal computation, have been successful in explaining a large set of behavioral data. However, it remains unclear whether the component operations postulated in these models correspond to any specific biological mechanisms. Using stimuli in different sensory modalities and manipulating physical properties known to bias the 'subjective' perception of time (speed for vision and pitch for audition), the present study aimed to highlight brain areas where activity correlates with the 'subjective' perception of time: a time accumulator according to clock-counter models. Using functional MRI we found that during the encoding of a temporal interval, the hemodynamic response of a few brain regions correlated with the interval reproduction performance. For the visual modality, the activity of the putamen, the insula and the mid-temporal cortex reflected the subjective interval duration, which was biased according to the different speeds of the visual stimuli. This effect was found only when subjects encoded the stimulus duration and was specific for the visual modality, where a significant overestimation of time with increasing speed was observed. These results demonstrate a definite relation between 'subjective time' and brain activity, supporting the hypothesis of a physiological correlate of time 'accumulation'.

G19 Effects of blue-enriched polychromatic light on ocular and electroencephalographic correlates of human alertness and melatonin

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Light exposure, particularly at the short-wavelength range, can result in numerous effects on the human circadian process via the non-imaging forming system. Here we investigated if commercially available compact fluorescent lamps with different colour temperatures can impact on subjective and objective measures of alertness, melatonin and cortisol levels in the evening. Sixteen healthy young men were studied in a balanced cross-over design with light exposure of three different light settings (compact fluorescent lamps with light of 40 lux at 6500K and at 2500K and incandescent lamps of 40 lux at 3000K) during 2h in the evening. Artefact-free EEG samples derived from eight derivations were subjected to spectral analysis. Additionally, ratings of sleepiness levels and salivary melatonin and cortisol measurements were collected every 40 minutes during the study. Exposure to light at 6500K induced a significant suppression of the evening rise in endogenous melatonin, together with increased subjective alertness. Cortisol levels and slow eye movement (an objective marker for sleepiness) were not affected by any of the light conditions. However, wake electroencephalographic (EEG) frontal activity in the frequency range of 8.5-10.5Hz and 12-14Hz was significantly reduced during exposure to light at 6500K (p at least <0.05). Our findings suggest that the sensitivity of the human alerting response to polychromatic light at levels as low as 40 lux, is blue-shifted relative to the three-cone visual photopic system. Thus, commercially available blue-enriched compact fluorescent lights impact on numerous aspects of human circadian physiology, and subjective and objective alertness levels.

G20 Born with an Ear for Dialects? Structural Plasticity in the Expert Phonetician Brain

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Are experts born with particular predispositions, or are they made through experience? We examined brain structure in expert phoneticians, individuals who are highly trained to analyze and transcribe speech. We found a positive correlation between the size of left pars opercularis and years of phonetic transcription training experience, illustrating how learning may affect brain structure. Phoneticians were also more likely to have multiple or split left transverse gyri in the auditory cortex than nonexpert controls, and the amount of phonetic transcription training did not predict auditory cortex morphology. The transverse gyri are thought to be established in utero; our results thus suggest that this gross morphological difference may have existed before the onset of phonetic training, and that its presence confers an advantage of sufficient magnitude to affect career choices. These results suggest complementary influences of domain-specific predispositions and experience-dependent brain malleability, influences that likely interact in determining not only how experience shapes the human brain but also why some individuals become engaged by certain fields of expertise.

G21 Single administration of levodopa modulates reward sensitivity but not self-control in a social decision making task

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In social interaction we oftentimes have to override self-interest to comply with social norms and group interests. Mainly two factors are decisive to succeed in such matter: First, the sensitivity to the reward assigned to the immediate self-interest, and second, the amount of cognitive capacity available to exert self-control. Thus, self-control failure may be caused by either insufficient self-control and/or an overwhelming temptation of immediate reward.

Clinical and experimental research suggests that the neurotransmitter dopamine is crucially involved in self-control and the processing of rewards. The precise role of dopamine, however, is still subject of debate; some argue that dopamine acts on the cognitive process of self-control itself, while others emphasize its role in reward processing and claim that dopamine may rather influence the sensitivity to reward.

In the present study, we attempted to experimentally tease apart the influence of dopamine on self-control and reward sensitivity by applying a social interaction task with two conditions involving real monetary stakes. We show that the double-blind, placebo-controlled administration of 300 mg L-dihydroxyphenylalanin (L-DOPA) to healthy male subjects (N=184) had no effect on self-control, but significantly increased reward sensitivity.

Although previous evidence suggests that dopamine is involved in both self-control and reward processing, our findings imply that the sensitivity to reward-related stimuli is more susceptible to changes in dopamine brain levels than higher cognitive control.

G22 Identifying and exploiting the electrophysiology of illusory body parts ownership and motor imagery

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Bodily ownership of fake, virtual, or prosthetic arms can be manipulated using the Rubber Hand Illusion. To investigate the electrophysiological changes associated with illusory ownership and their relationship to motor imagery, we recorded 64-channel electroencephalography (EEG) while inducing illusory ownership of two virtual arms in a virtual reality/haptics setup.

Participants saw (head-mounted display) one of two virtual objects (arms, non-body cylinders) projecting from their shoulders into different positions than their real arms. Visuo-tactile stimulation was provided in a spatiotemporally synchronous or asynchronous manner by vibration motors affixed to the (unseen) left and right hands and animation of corresponding virtual motors on the virtual hands. A second study involved performing a cued motor imagery task (left/right hand clasping) while receiving such visuo-tactile stimulation.

Illusory ownership for the virtual arms was reported only during synchronous visuo-tactile stimulation on the virtual arms (illusion case). Spectral EEG analysis revealed a body-selective, synchrony-dependent modulation of the μ -band rhythm over bilateral sensorimotor cortex and was confirmed by localization of the neural generators to the left and right post-central gyrus (sLORETA). Furthermore, μ -band power correlated with the reported strength of the illusion, but only in the illusion case.

Cortical regions associated with μ -band modulation during motor imagery showed strong spatial overlap with those found for illusory ownership. Combining motor imagery with the different visuo-tactile schemes led to significant changes in μ -band power for all experimental conditions except for the illusion case, further suggesting μ -band power as a robust, invariant electrophysiological signature of body ownership. Finally, we demonstrate a promising application of our findings by enhancing classification performance in a traditional brain-computer interface.

G23 Musical syntax processing as a function of musical expertise – Part 1: Spatio-temporal ERP analyses and source imaging.

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Previously, comparing professional pianists to non-musicians, we showed early expert specific ERP topographies or "microstates" of information processing in response to harmonic transgressions at musical closure in expressive tonal music. In the current experiment we investigated 3 levels of expertise, comparing expert pianists (E), amateur pianists (A) and non-musicians (N), and presented musical pieces with 3 levels of harmonic transgression at closure consisting in subtle (T1) and apparent (T2) transgressions intertwined with pieces ending regularly (R). We used 90 original digitally controlled expressive musical pieces, all appearing in R, T1 and T2 conditions (n=270). Subjects indicated whether pieces ended correctly or not. Behavioral analyses on d-prime, a sensitivity index, for T1 and T2, yielded Expertise x Transgression interaction, and revealed different sensitivity patterns for all expertise levels. A held an intermediate position. However, T1 sensitivity massively separated E from both A and N. Results of spatio-temporal ERP analyses on duration of microstate occurrence, in a 290-480ms window after stimulus onset, matched the behavioral results. Expertise x Microstate interaction revealed expert specific microstates. Expertise x Transgression x Microstate interaction showed gradual differences between levels of expertise for the occurrence of microstate maps grouping A and E against N for T2, and E against A and N for T1. The most dominant expert specific microstate exhibited focal frontal positivity and widely distributed posterior negativity. Its estimated sources originated in bilateral premotor, rostromedial prefrontal and right paralimbic regions, reflecting respectively audio-motor coupling and relevance detection in the context of harmonic syntax processing. Brain activations seem to increase in these areas with degree of musical aptitude.

G24 Probabilistic reversal learning in mice: establishing a task and assessing serotonin effects using genetic and pharmacological methods

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Depression psychopathology includes both increased emotional sensitivity to negative events/stimuli and reduced emotional sensitivity to positive events/stimuli. Given that negative events can include non-delivery of expected positive stimuli, then the punishment and reward systems are inter-related. Dopamine is a major modulator of reward and there is growing evidence that serotonin is a major mediator of punishment, possibly including non-delivery of expected reward. The probabilistic reversal learning (PRL) task measures subjects' sensitivity to non-delivery of an expected reward i.e. "negative feedback sensitivity" (NFS). NFS is increased in depression and following (tonic) serotonin reduction. Whilst the human PRL task can be combined with neural imaging to study the neurobiology of NFS, a valid PRL task in animal species, and particularly in mouse, would allow for detailed experimental study of the neurobiological and pharmacological regulation of sensitivity to NFS. Here we present the first PRL task in mouse, and the effects on mouse behaviour in this task of genetic and pharmacologic manipulation of serotonin function, using a 5-HT transporter (5-HTT) knockout mouse and the SSRI antidepressant escitalopram, respectively. We demonstrate that heterozygous 5-HTT knock-out mice exhibit reduced NFS relative to wildtype littermates and that acute treatment with escitalopram also results in reduced NFS. Therefore, both genetic and pharmacological manipulations that reduce serotonin transporter function lead to reduced negative feedback sensitivity. Increased tonic serotonin availability/signalling could be a common mechanism mediating these effects.

G25 Prediction of exploratory decision-making from single-trial topographic EEG analyses

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Decision-making in an uncertain environment is driven by two major needs: exploring the environment to gather information or exploiting acquired knowledge to maximize reward. The processes underlying exploratory decision-making have been mainly studied by means of functional magnetic resonance imaging leaving their temporal aspects under-explored. Here, we use a well-known gambling paradigm in reinforcement learning to assess the neural correlates of exploratory decision-making. The aim is to predict subjects' decisions on the next trial and to detect when this decision is taken. To establish this prediction, we classified single-trial EEG voltage topographies during reward evaluation. Because the timing of the decision varies across trials, we extracted non-time-locked topographies and evaluated when there was sufficient evidence to reliably predict the subject's choice. Classification accuracy for seven subjects, measured as the area under the Receiver Operator's Characteristic curve, was on average 0.65. On an individual subject basis, distributed source estimations were performed on the topographies extracted in order to statistically evaluate the neural correlates of decision making. For trials leading to exploration, there was significantly higher activity in dorsolateral prefrontal cortex and in the right parietal supramarginal gyrus; areas known to be responsible for task-switching and in modulating behavior under risk and deduction. No area was more active during exploitation, further supporting the theory that exploration overrides exploitative tendencies. We show for the first time the temporal evolution of differential patterns of brain activation in an exploratory decision-making task on a single-trial basis.

G26 Motor evoked potentials during repeated presentations of environmental sounds

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Representations of concepts are distributed within the brain (Pulvermüller, 2005). Hearing environmental sounds related to manual actions can facilitate motor evoked response induced by transcranial magnetic stimulation (TMS) single pulse to the hand motor cortex (Aziz-Zadeh et al., 2004). Moreover, neurophysiological responses to a stimulus can change while the stimulus is repeated (e.g. repetition suppression), indicative of plasticity of the brain activity (Grill-Spector et al., 2006; Murray et al., 2008). The present study investigated the impact of stimulus repetitions on mechanisms of repetition-induced plasticity as indexed by motor evoked potentials (MEPs) following a TMS single pulse to the hand motor cortex, while listening to environmental sounds. Repetition priming was investigated for MEPs associated with the presentation of hand-related action sounds vs. non hand-related action sounds (i.e. factor of sound type) and with respect to the initial vs. repeated presentation of the sound (i.e. factor of presentation). The MEPs were recorded from the first dorsal interosseus of both hands and each sound was presented twice within each recording side (left vs. right hand with the corresponding hand motor cortex TMS-stimulation). The results indicated an interaction effect of sound type by presentation for MEPs recorded from the left hand (right hemisphere TMS-stimulation). The MEPs associated with hand-related action sounds showed adaptation (i.e. repetition suppression) compared to the MEPs associated with non hand-related action sounds. We discuss our results in terms of specialized neural network involved in sound processing, which is characterized by repetition-induced plasticity and may be involved in imitation learning.

G27 Musical syntax processing as a function of musical expertise - Part 2: fMRI analyses

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In cognitive neuroscience musical syntax processing is classically examined by electrophysiological methods (Maess et al., 2001; James et al., 2008). Here we present a functional magnetic resonance imaging (fMRI) study, which investigated musical expertise dependent brain activations in response to graded harmonic transgression in western tonal phrase closures. As stimuli we used ad hoc composed pieces for string quartet with manipulated last chords according to three conditions: regular endings, subtle harmonic transgressions and apparent harmonic transgressions. Each condition was represented by 30 different musical pieces in all minor and major tonalities (for more details see part 1 of our multimodal study (James, 2011)). Sparse temporal sampling design for image acquisition allowed to present the musical stimuli within resulting silent periods, thus under optimal conditions to decode the harmonic structure of the auditory material. Three balanced groups of participants – piano experts, piano amateurs and non-musicians – responded whether the musical pieces ended correctly or not. The analyses presented here are results of the following full factorial design (SPM8): 2-way ANOVA Expertise x Transgression. The contrasts used eliminate all activations associated with basal auditory processing and task related motor responses. The behavioral results show significant differences with respect to rater sensitivity (d') as a function of musical expertise and transgression level. An additional independent behavioral experiment based on proximity ratings of chord pairs, analyzed by non-metric multidimensional scaling (NMDS) confirmed an expertise dependent potential for harmonic chord processing (Oechslin, under revision). Whole head fMRI data analysis by 2-way ANOVA revealed a robust main effect for Expertise in the right superior frontal – intraparietal network, which has been linked to visuo-spatial and auditory working memory (Klingberg, 2006; Schulze et al. 2010, 2011): a linear decrease of activation (superior frontal gyrus (SFG) and inferior parietal lobe (IPL)) in association with increased musical expertise evidences either lower involvement (lower task difficulty for musicians) or increased efficiency of neural WM strategies in musicians. Moreover, main effect Transgression and interaction Expertise x Transgression revealed activation clusters in bilateral anterior insula and right inferior temporal gyrus (pars opercularis). The former is suggested to be modulated especially by emotional aspects of syntactic musical structure, whereas the latter has been shown to be strongly involved into the detection of musical syntax violations (Tillmann et al., 2006; Koelsch et al., 2005). We conclude that musical training alters the processing of harmonic transgressions by modulating activation in regions associated with working memory (IPL-SFG network), relevance detection and decision making (anterior insulae) as well as in the right IFG (pars opercularis), known as a pivotal area for auditory attention and syntax processing.

G28 Effects of Pulse-Modulated Mobile Phone-Like Fields and Pulsed Magnetic Fields on the Human Sleep EEG

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Previous research showed that pulse-modulated radio frequency electromagnetic fields (RF EMF) emitted by mobile phones alter brain physiology during sleep. Nevertheless, it remains unclear which components of the RF EMF signal are responsible for the alterations of sleep EEG power. We recently showed that the 14 Hz pulse modulation component, which is in proximity of physiological sleep spindles, is a possible mediator of sleep EEG alterations. However, further results also indicated that other modulation components outside of the spindle frequency range appear to have an influence on the sleep EEG. Furthermore, a possible contribution of higher harmonics of the modulation frequency could not be excluded. In the present study we employed a magnetic field exposure and an RF EMF exposure pulse-modulated at low frequency with considerably attenuated higher harmonics, in order to determine whether the low modulation components are sufficient to elicit an effect, or whether the effect only occurs when applied in combination with RF EMF. In a randomized double-blind cross-over design, twenty-five young healthy men were exposed at weekly intervals to three experimental conditions for 30 minutes before sleep:

(1) RF EMF pulse-modulated at 2 and 8 Hz (carrier frequency: 900 MHz; specific absorption rate: 2 W/kg); (2) a magnetic field pulsed at 2 and 8 Hz (pulse sequence identical to (1)); (3) sham condition (no field). During exposure, subjects performed three different cognitive tasks. Following exposure, night-time sleep was recorded. During NREM sleep, power in the spindle frequency range was increased following exposure to pulse-modulated RF EMF. Additionally, increased spectral power in the delta and theta frequency ranges was observed following both exposure conditions compared to sham. Consistent with previous research, pulse-modulated RF EMF affected EEG power in the spindle frequency range. Additionally, our results suggest that pulsed magnetic fields also appear to alter brain physiology. These findings highlight the importance of pulsing in the influence of EMF on the human brain.

G29 Temporal dynamics of brain activation of biologically-relevant stimuli

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There is a great body of literature investigating the neural basis of emotion processing using neutral and emotionally expressive faces. It is reported that emotional faces are processed differently from neutral ones when presented outside the focus of attention as well as when presented subliminally. This EEG study disentangles the temporal dynamics of supraliminal as well as subliminal processing of supposedly more salient and biologically relevant stimuli like nude people. To this end, photographs of dressed and naked bodies were presented to 20 healthy control subjects in a backward masking paradigm for 16ms (subliminal) and 260ms (supraliminal) conditions. The processing of pictures of bodies in the absence of awareness elicits an enhanced positivity on lateral and middle occipital as well as inferior-occipital-temporal areas on the early P1 (peaking at 100ms) as well as P2 component compared to the conscious processing of the same stimuli. Within category, pictures of naked bodies produce an enhanced processing compared to dressed bodies in the supra- as well as subliminal condition on the occipital N1 (peaking at 160 ms). This strongly suggests an effect of differential processing of sexual features compared to neutral, dressed bodies in healthy control subjects.

G30 Long – range integration of emotional prosody and spatial attention is underlined by amygdalo – orbitofrontal synchronization in humans

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Detection of potentially relevant events in the environment may occur at different levels of processing, including processes being engaged relatively independently of attention and other being dependent on voluntary attention and task demand. The purpose of this study was to investigate to what extent the anatomical connectivity between amygdala and orbitofrontal cortex (OFC) might underlie the functional integration of attended and unattended processing of emotional prosody. In order to manipulate spatial attention orthogonally to emotional prosody, we used a dichotic listening paradigm, requiring the patients to perform a gender decision task. By using intracranial macro electrodes, LFPs were recorded within the right amygdala (AMG) and the lateral and medial parts of OFC in two epileptic patients as potential candidate to a brain surgery. Phase-locking measures were used to test the neuronal communication between these time series of AMG and OFC brain signals. Our results showed that the processing of unattended compared with attended emotional prosody and neutral one triggered an onset-locked enhanced functional coupling between AMG and medial OFC mainly in the beta frequency band. In contrast, our data revealed a significant early increase of the phase-locking synchronization between AMG and medial OFC in the theta frequency range for the voluntary processing of angry prosody as compared with unattended emotional prosody and neutral prosody. These results highlight that the AMG-medial OFC network might be involved in encoding the emotional value of a stimulus by underlying early relevance-detection processes.

G31 Eyes like it, brain likes it: Tracking the neural tuning of cultural diversity in eye movements for faces

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Eye movement strategies deployed by humans to identify conspecifics are not universal. Westerners preferentially fixate the eyes and mouth during face recognition, whereas strikingly Easterners focus more on the central facial region. However, when, where and how Preferred Viewing Locations (PVLs) for high-level visual stimuli are coded in the human brain has never been directly investigated. To this aim, we simultaneously recorded eye movements and electroencephalographic (EEG) signals of Western and Eastern observers while they performed face identification of learnt identities. To avoid complex EEG artifacts generated by multi-oriented saccades, we defined 9 equidistant Viewing Positions (VPs) covering the internal facial features and presented the faces centered on a random VP for 100ms, hence controlling for foveal and extrafoveal information sampling. The fixation maps extracted from a prior free-viewing condition corroborated cultural diversity in PVLs despite similar behavioral performance. Conventional component-based electrophysiological analyses revealed only sensitivity to VPs on the P1 component. However, to properly establish potential modulations of EEG signals as a function of PVLs, we extracted the average Z-scored fixation intensity from the fixation maps around non-overlapping VP regions (VPZs). Then, we computed a component-free data-driven spatio-temporal regression between the VPZs and EEG amplitudes. This novel approach revealed, in both groups of observers, a marked direct relationship between VPZ fixation intensity and the amplitudes of the EEG around 350ms over the well-defined face-sensitive N170 network: the greater the VPZ, the larger the EEG amplitudes on the matching VPs. This effect was unrelated to a burst of microsaccades occurring in this time window. Our data show that cultural fixation preferences for faces are related to identical post-perceptual neurophysiological responses over the occipito-temporal cortex. Humans from different cultures deploy distinct eye movement strategies, but they crucially rely on a universal neural tuning.

G32 Intermale aggression and coping style in RHA/RLA rats

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Roman High-(RHA) and Low-(RLA) avoidance rats have been selected according to their good (RHA) or bad (RLA) performance in learning a two-way, active avoidance task in the shuttle-box. These two lines differ in stress reactivity (the neuroendocrine stress response is exaggerated in RLA, blunted in RHA rats), trait anxiety (RLA are more anxious than RHA rats) and coping style (RHA are proactive individuals, RLA rats are more reactive and behaviourally inhibited). A number of studies in various species have shown a direct relationship between coping style and aggressiveness: active copers are also more aggressive individuals. Intermale aggression was measured in RHA/RLA under various circumstances. As compared to wild rats, these lines (derived from Wistar rats) usually show low levels of aggressive behaviour in their normal home environment. However, when adult males paired with a female for 20 days for breeding are returned to a new cage with another male partner (from the same line), fights do occur. As expected, RHA rats showed a shorter attack latency (the usual measure of aggressiveness) and a larger number of attacks as compared to their RLA counterparts. Fights may also occur when the bedding is changed in cages containing two or three males (standard housing conditions in our animal facilities). The same line-related differences were found under these conditions, although the levels of aggression were much lower. Finally, it was found that conditions of frequent social mixing (i.e. a rather unstable social environment) during the peripubertal period could affect aggressiveness by increasing the number and the severity of attacks, but not attack latency. It is concluded that attack latency depends mainly on the genetic background, but that other aspects of aggressiveness can be modulated by environmental factors.

G33 Development of a mouse model for the study of specific and generalized “helplessness”, a major concept in depression

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Emotional-cognitive control over aversive events underlies mental health, and loss of such control and generalized helplessness are of major importance in theories and treatment of depression and anxiety disorders. Animal models of impaired emotional-cognitive control are essential for the study of the circuitry and etio-pathophysiology of this mental state. Establishing an animal model of generalized loss of aversive control requires two basic components: (1) A behavioural assay that detects impaired control over aversive stimuli. (2) An environmental manipulation that induces a robust behavioural deficit in this assay, and where the manipulation takes a different form of aversive stimulation from that used in the assay. Here we present our development to-date of such a two-stage model in C57BL/6 mice. (1) Mice were exposed to two daily sessions of escapable electro-shock (ES) or the same duration of inescapable e-shock (IS) in a two-way escape arena. Both groups were then tested under ES conditions, and IS mice exhibited a consistent 2-way escape deficit. (2) Naïve mice were screened for high levels of e-shock escape behaviour and allocated to chronic social defeat (CSD) or control (CON): For 15 days, CSD mice were exposed physically to an aggressive CD1 mouse for 10 min/day and maintained in visual and olfactory contact throughout the day. CSD mice developed IS-like behaviour in terms of 2-way escape deficit, whereas CON mice maintained high levels of escape responding. CSD mice also exhibited high levels of freezing, high body-weight variability and enlarged adrenal glands, relative to CON mice. A pilot study to investigate the effects of repeated IS on c-FOS expression, demonstrated increased c-FOS density at 120 min post-IS in the infralimbic cortex, dorsal raphe nucleus and amygdalar nuclei. This mouse model of generalized loss of aversive control will be studied to elucidate the circuitry and etio-pathophysiology of this emotional-cognitive state and to identify novel targets for its neuropharmacological reversal.

G34 Genome-wide Analyses of the Transgenerational Impact of Early Life Stress in Mice

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Stressful experiences early in life constitute risk factors for the development of behavioral and emotional disorders such as cognitive impairments and major depression. The etiology of these brain pathologies has been suggested to largely involve non-genetic factors. To examine the importance of these factors, we developed a mouse model that captures both genetic and environmental components. In this model, mouse pups are subjected to unpredictable maternal separation and maternal stress (MSUS) during their early postnatal life. This manipulation impaired cognitive functions and induced depressive behaviors in the animals when adult. Further, these behavioral alterations were transmitted to the following offspring (F2). We investigated the impact of MSUS on gene expression in the hippocampus of F2 mice using Roche NimbleGen microarrays, and on DNA methylation using methylated DNA immunoprecipitation assays (MeDIP) in combination with Deluxe Promoter arrays from Roche NimbleGen. Signal transmission pathways were identified as being affected by MSUS treatment in F2 mice. Consistently, follow-up electrophysiological experiments demonstrated that synaptic plasticity, in particular long-term potentiation in the hippocampus, was impaired in F2 MSUS mice. These mice also had impaired memory performance on a contextual fear memory task. These results highlight the strong impact of early stress on cognitive functions, behavior and brain plasticity.

G35 Secondary sexual traits in human male and female bodies: electrophysiological and behavioral studies.

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Waist-to-hip ratios (WHR) and waist-to-shoulder (WSR) ratios are defined as human secondary sexual traits. They appear to influence the attractiveness, probably because they convey information about reproductive/genetic potential. We performed a behavioral (rating) test and an ERP study on a group of right handed heterosexual healthy participants, half men and half women, viewing female models with four different WHRs (0.6, 0.7, 0.8 and 0.9), and male models with four different WSRs (0.5, 0.6, 0.7 and 0.8). In the behavioral experiments participants had to rate the attractiveness of 192 pictures of women and 96 pictures of men. In the EEG experiments (go, no-go task), subjects were presented with stimuli, comprising female or male bodies, as well as distracter targets (pseudo-animals), to which they were asked to respond manually. In the WHR experiment, naked bodies elicited a greater negativity (N190) than dressed ones over the left occipital-temporal electrodes in male subjects compared to females. But in both experiments, the occipital P1 (135 ms) was sensitive to WHR and WSR, showing a different pattern of activation between male and female groups. Moreover, behavioral results showed the same trend of WHR preference for men and women, but a different trend of WSR preference; in addition, naked bodies are more sexually attractive than dressed ones. All these results substantiate the hypothesis that WHR and WSR are measures of physical attractiveness. On the other hand, ERPs data support the hypothesis that the N190 is more sensitive to whole body shapes than body parts compared to P1 appearing to respond mainly to body features, such as WHRs and WSRs. This indicates a very rapid processing of these secondary sexual traits in the perception of female and male bodies.

G36 Valid, sensitive, interpretable: A new approach to EEG analysis

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Relative to other neuroimaging methods in human research, EEG has gradually gained its complexity. Over the years, advances in EEG technology have allowed for an increased number of sensors to be recorded from, a higher sampling rate, and a broader range of experimental manipulations. Despite such depth in data acquisition, methods with which to analyse evoked potentials have remained relatively primitive and border on statistically invalid, difficult to interpret, and insensitive. Here, arguments are made for a non-parametric, permutation approach to EEG analysis which: uses information from all channels and every time point; can incorporate any statistic; is statistically valid; combines intensity and cluster information optimally; and eliminates the need for user assumptions and interference. In order to maximise sensitivity, threshold-free cluster-enhancement (TFCE) is used which is based on a novel algorithm to calculate channel neighbours in time and space. This novel analysis method is compared with previously used methods both theoretically and with relevant practical examples for single case and group studies. For all datasets the TFCE approach generally outperforms the classical maximal intensity approach, parametric SPM approach, most cluster-based methods, and is comparable to even the most finely tuned cluster approach using just TFCE's default parameters. Moreover, the TFCE approach retains information on the local maxima within significant clusters and provides an individual p-value for each channel-time pair. In conclusion, the non-parametric permutation approach guarantees statistical validity while the TFCE approach maximises sensitivity and interpretability with minimal opportunity for user bias.

G37 Wake-up morning light improves cognitive performance after sleep restriction

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Light exposure elicits numerous effects on human physiology and behaviour; however it remains inconclusive whether the timing of light exposure, particularly at daytime, impacts on cognitive performance following partial sleep restriction. Thus, we investigated if wake-up morning light can counteract the effects of sleep restriction on cognitive performance. Twenty healthy young men (20-35 years) completed the field part of the study, which comprised actigraphy monitoring and sleep diaries to characterize habitual sleep and wake timing during three consecutive weeks. Currently, 9 participants (from 17 planned) have completed the in-lab part of the study, which consists of a balanced cross-over design with light exposure after partial sleep restriction (i.e. 8 hours of a sleep episode curtailed to 6 hours). Three different light settings were utilized each time: blue light (20 minutes exposure after wake-up; 200 lux of 470nm light); simulating dawn light (polychromatic light gradually increasing from 0 to 250 lux during 30 minutes before wake-up time, the light remains around 250 lux for 20 minutes after wake-up time); dim light (<8 lux). Cognitive tests were performed every 2 hours during the wake episode and included the Sustained Attention to Response Test, Paced Visual Serial Addition to Task, Motor Tracking Test and the verbal 1-, 2- and 3-n back test. A cognitive composite score for these tests was used in the analysis. During wake-up time until nearly 8 hours of elapsed time awake, the cognitive composite score was similar irrespective of light settings. Interestingly, after 12 hours of elapsed time awake, cognitive performance significantly deteriorated following the morning dim light exposure ($p < 0.01$). Conversely, cognitive performance was increased after 12 hours of time awake, following both morning simulating dawn light and the morning blue light ($p < 0.01$). These differences in cognitive performance between the two light settings and the dim light condition persisted until approximately 16 hours of elapsed time awake. Morning wake light devices can impact on cognitive performance, such that it remains stable throughout the day, despite the effects of higher sleep pressure induced by sleep restriction. On a broader context, these light conditions may provide an effective rationale for enhancing performance in individuals who experience sleep restriction.

G38 Auditory Perception with Neuromorphic Chips

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Audition and vision are the two main sensory modalities through which we perceive the world around us. But auditory perception unfortunately is not as well understood as visual perception. It is not clear yet to what extent an analogy between the structure and function of the early visual processing areas and the auditory processing ones is possible. The inherent temporal dynamics of sounds do not allow for a direct application of the many classical visual processing paradigms that have been developed up to now.

Within this context, we are investigating the characteristics of auditory perception in humans and rodents, and developing neuronal models. Rather than using computer simulations, we are implementing these models using neuromorphic analog VLSI chips. This technology allows us to experiment with real-time behaving artificial systems that have biologically realistic parameters and that share many constraints in common with their biological counterparts (such as limited resolution, noise, and inhomogeneities).

We are applying these VLSI models to the study of multi-stable perceptual phenomena, a form of perceptual phenomena in which there are unpredictable sequences of spontaneous subjective changes. While usually associated with visual perception, such phenomena are also found for and auditory percepts. Stimulus-specific adaptation (SSA) is a phenomenon observed in auditory neural systems which occurs when the spike count elicited in a single neuron by external stimuli decreases with repetitions of the same stimulus, and recovers when a different stimulus is presented. SSA therefore effectively highlights rare events in stimulus sequences, and suppresses responses to repetitive ones. We propose a model of SSA based on synaptic depression and describe its implementation in neuromorphic analog VLSI technology. We examined the effect of input parameters upon SSA and showed that the trends apparent in the results obtained in-silico compare favorably with those observed in biological neurons.

Our long-term goal is to engineer a biologically plausible real-time behaving system that can respond to sounds from the surroundings, exhibiting the same properties and dynamics of the auditory systems they model.

G39 Changes in sleep EEG at moderate altitude

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Several studies reported a shift towards lighter sleep with an ascent to high altitude, based on visually scored sleep stages. Changes in sleep resulting from exposure to moderate altitude, however, are difficult to detect. The aim of the present study was to investigate whether EEG power spectral analysis would be a sensitive tool to determine potential sleep EEG changes at two different levels of moderate altitude and, moreover, whether such changes occur in a 'dose-dependent' manner. In a randomized cross-over design, 51 healthy young men spent one baseline night at 490 m and two consecutive nights at each higher altitude (1630 m and 2590 m). Polysomnographic recordings including frontal, central and occipital EEG derivations were conducted in all five nights with time in bed restricted to 7 hours. Power density spectra were calculated for 30s epochs (FFT; average of six 5-s epochs; frequency resolution 0.2 Hz) and averaged over the minimal common length of non-REM sleep within individuals. Only 44 participants with sufficient sleep efficiency (80%) at baseline and in the first recording entered the analysis. Preliminary analysis revealed that exposure to hypobaric hypoxia at an altitude of 2590 m resulted in decreased EEG spectral power in the lower frequency range (delta: 0.8-4.6 Hz, theta: 4.6-8 Hz; frontal and central derivations). At 1630 m only delta activity was decreased (frontal derivations). Furthermore, delta activity in frontal derivations was reduced in an altitude dependent manner: At the highest altitude by -12.9 and -14.0% and at 1630 m by -4.5 and -0.7% (first and second night, respectively). Delta activity - a reliable marker of sleep intensity and sleep homeostasis - was reduced at altitude which leads to increased sleep propensity that might impinge on sleep intensity in the following nights.

Supported by the Zurich Center for Integrative Human Physiology and Schweizerische Unfallversicherungsgesellschaft.

G40 Distinction of posed and genuine emotional expressions under high and low task relevance

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The ability to distinguish between posed and genuine expressions of emotion and to act accordingly is a fundamental social skill. To investigate the neural correlates underpinning this sensitivity, we used fMRI to compare regional changes in brain activity associated with viewing posed and genuine facial displays of happiness and sadness under two conditions in which we varied the sensitivity's task relevance. Photographs of facial displays were presented individually to 7 right-handed female volunteers. Each participant judged in a first run whether the person was "showing" the target emotion (low task relevance) and in a second run whether the person was "feeling" the target emotion (high task relevance). Results for the feel condition showed activity increases in the medial superior frontal and angular gyri during the observation of genuine compared to posed displays. Genuine displays of sadness were also accompanied by higher activity in prefrontal and premotor areas, whereas those of happiness were accompanied by higher activity in the middle cingulate and parietal cortex. Results for the show condition showed activity increases in the inferior frontal gyrus for genuine sad displays, and in the middle cingulate cortex and superior frontal gyrus for genuine happy displays, as well as activity decreases in a more anterior region of the middle cingulate cortex and the postcentral gyrus. These results not only suggest the involvement of specific brain regions in the processing of posed versus genuine facial displays of emotion, but provide first neural evidence for the importance of distinguishing these types of displays in future research. In addition, the differential processing of posed and genuine emotional expressions even under low task relevance points to the biological importance of the information they each provide.

G41 The Effects of Visual Feedback Manipulation in Virtual Reality on Cortical Activity: A Pilot Study

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It is known that visual feedback has an influence on the performance of stroke patients executing virtual reality-mediated rehabilitation tasks. However, there are few studies which directly investigate the effects of visual feedback manipulation on neural activity changes. In the present study we created an experimental setup for investigating cortical activity during systematic visual feedback manipulation of finger movements. We performed tests with healthy subjects who performed a line-tracking task under four conditions manipulating visual feedback of their own hand. To investigate hemodynamic responses in motor areas during the line tracking task we used functional near-infrared spectroscopy (fNIRS). We predicted that viewing larger or smaller virtual movements of fingers, compared to the real movements, would affect activity in motor areas and thus the hemodynamic response. Our preliminary results showed changes in the hemodynamic responses between stimulation period and baseline. There were indications of possible differences between conditions, and also of adaptation effects within conditions. We discuss the implications of our results for the use of virtual reality in neurorehabilitation.

G42 Trait-like spindle activity, information processing speed and their association to sleep-dependent performance improvement

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Introduction Studies show that higher sleep spindle activity is reflected in higher intellectual ability (e.g. Geiger et al., 2011; trait-like aspect of sleep EEG). Moreover, spindle activity during sleep was increased after learning specific tasks and this state-like increase correlated with the overnight performance improvement (e.g. Gais et al., 2002). The question arises how trait-like spindle activity and general cognitive ability are associated with sleep-dependent performance improvement.

Method 15 male adolescents (18-20 years) were trained on a semantically unrelated word-pair task in the evening right before they were allowed to sleep. All night EEG was recorded and spindle activity (EEG power band 12-15 Hz, C4) during NREM sleep was calculated. In the morning they were retested on the task to verify sleep-dependent performance improvement and we assessed their general cognitive ability, i.e. information processing speed (ZVT, Oswald and Roth, 1987).

Results In an immediate recall before sleep subjects correctly recalled 14.0 (\pm 3.8 SD) out of 30 word pairs. During the delayed recall in the morning they showed a significant performance improvement ($+4.6 \pm 1.9$, $P < 0.001$). Information processing speed (1.5 ± 0.3 1/s) and spindle activity ($9.5 \pm 4.5 \mu V^2$) were correlated ($r = .55$, $P < 0.05$). In addition, there was a strong negative correlation ($r = -.77$, $P < 0.005$) between spindle activity and the overnight improvement in the number of recalled words.

Conclusion Our results show that lower spindle activity is associated with a higher potential for sleep-dependent performance improvements in this declarative learning task. This result is in contrast with other studies. E.g., according to Schabus et al. (2008) behavioural performance improvement after a night of sleep was not related to trait-like spindle activity. Differences in the behavioural task difficulty might explain this divergence.

G43 Model-based analysis of learning and memory in a genome-wide association study

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Individuals differ in how effectively they encode new information, recall old memories, or exploit their knowledge in decision making. There is substantial evidence that genes are involved in the regulation of human learning and memory; however, which genetic loci affect which specific cognitive processes is largely unknown. Approaches that use computational models to infer specific cognitive parameters from behavioural data and relate them to neural correlates and genetic differences are particularly suited for addressing this question. In this genome-wide association study (GWAS) we explored the relationship between human single nucleotide polymorphisms (SNPs) and computational parameters relating to knowledge acquisition, decision making, emotional modulation, and forgetting. The individual parameters were extracted by fitting a simple computational learning & memory model to actual human performance in a word learning and free recall task. The results revealed a highly significant association between a SNP in a brain expressed gene and the negative modulation parameter. In a different task – picture learning and recall – carriers of different variants of this SNP showed different memory of negative pictures and also had different locus coeruleus and parahippocampal activations in fMRI. In general, our study provides a hypothesis-free methodology for identifying genes that are potentially related to specific cognitive processes and lead to specific differences in behavioural phenotype.

G44 Processing of subliminal and unattended stimuli: an ERP study

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A number of investigations have reported that emotional faces can be processed subliminally, and that they give rise to specific patterns of brain activation in the absence of awareness. Recent event-related potential (ERP) studies have suggested that electrophysiological differences occur early in time (<200ms) in response to backward masked emotional faces. These findings have been taken as evidence of a rapid non-conscious pathway, which would allow threatening stimuli to be processed rapidly and subsequently allow appropriate avoidance action to be taken. However, for this to be the case, subliminal processing should arise even if the threatening stimulus is not attended. This is not yet been clearly established. In this ERP study, we investigated whether subliminal processing of fearful faces occurs outside the focus of attention. Fourteen healthy participants performed a line judgement task while fearful and non-fearful (happy or neutral) faces were presented both subliminally and supraliminally. ERPs were compared across the 4 experimental conditions (i.e., subliminal and supraliminal; fearful and non-fearful). The earliest differences between fearful and non fearful faces appeared as an enhanced posterior negativity for the former at 170ms (the N170 component) over right temporo-occipital electrodes. This difference was observed for both subliminal ($p < .05$) and supraliminal presentations ($p < .01$). Our results confirm that subliminal processing of fearful faces occurs early in the course of visual processing, and more importantly, that this arises even when the subject's attention is engaged in an incidental task.

G45 Sensory Motor Training Station with ARMin Robot to Improve Hand Eye Coordination

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Technology Assisted Therapy has the potential to transform rehabilitation options available, and to dramatically increase the reach of today's healthcare system. A new Sensory Motor Training Station (SMTS), a multi-purpose research and training system, has been designed and developed to offer more opportunities to provide the nervous system with sensory experiences that are very realistic. The system includes virtual reality, real objects, and robot support for upper limb manipulation training. SMTS design is based upon the principle that sensory experience and practice improve outcome more than either one independently. Visual sensory stimulation including a virtual limb is displayed on a semi-transparent mirror in a first person perspective in the position where objects will be viewed and touched for realistic interaction during robot assisted exercise. The ARMin 7 DoF robot is used in either Active or Passive mode and provides assistance as needed. Through task design, movement intention, motor assistance, and sensory experience are synchronized and modulated for intensive repetitive task-oriented exercise necessary for cortical reorganization through plasticity. Practice conditions may be adapted in difficulty as the trainee skills change. The robot measures kinematics and system software measures performance. In an arm location task, the upper limb is moved to a target location, pointing to a cue, or touching a real object. The robot moves the limb, or the person moves his or her own limb to the target with robot support against friction and gravity. Then while the natural limb is concealed, through a sequence of prompts the person identifies the location of his or her limb as an exercise to improve arm location recognition and manipulation skills.

G46 Novel object recognition test in tree shrew (*Tupaia belangeri*)

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Novel object recognition test has widely been used in rodents to examine recognition memory. Here, we examine novelty preference using the NOR task in tree shrew, a small animal species that is considered to be an intermediary between rodents and primates. Our paradigm consisted of three phases: arena familiarization, training sessions with two identical objects in the arena and a test session following a 24-hour retention period with a familiar and a novel object in the arena. We employed two different training durations: one and three sessions on consecutive days. After three training sessions, tree shrews exhibited robust preference for novel objects on the test day. This was accompanied by significant habituation in familiar object exploration, occurring largely between the first and second day of the training phase. By contrast, tree shrews did not show a significant preference for the novel object after a one-session training. Nonetheless, they spent significantly less time exploring the familiar object on the test day compared to the training day, indicating that they did maintain a memory trace for the familiar object. Our study showed different time courses for habituation and the emergence of novelty preference, suggesting that novelty preference is dependent on well-consolidated memory of the competing familiar object. Taken together, our results reveal robust novelty preference of tree shrews, in general similarity to previous findings in rodents and primates.

G47 Circadian and homeostatic influences on sequence learning are affected by age

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Procedural learning refers to the acquisition and consolidation of perceptual-motor skills affecting behaviour without necessarily requiring conscious recollection. The effects of aging on the ability to form procedural memories are still controversial, though it appears to have a differential effect upon acquisition and consolidation. In young adults, circadian and sleep-wake dependent modulations have been reported for skill detection. Since aging is characterized by changes in sleep-wake regulation, it may be assumed that circadian phase and sleep pressure affects procedural memories differentially in older people. Here, 8 old and 12 young adults completed a sequence learning task throughout a 40-hour sleep deprivation (SD) protocol under controlled laboratory conditions. Procedural memory performance was assessed by contrasting reaction times (RTs) between sequenced (S) and random (R) trials [(S-R)/R]. Performance was tested at 6 times: evening at 10 p.m. before baseline night, evening after baseline night and sleep deprived night, morning at 9 a.m. after baseline night, after sleep deprived and recovery night from SD. Preliminary results indicate that learning occurred both in the young and elderly as indicated by faster RTs in S compared to R trials in both age groups ($p < .001$). However, a significant main effect of the factor age was observed, indicating better performance in young relative to the elderly ($p < .05$). Importantly, procedural memory was affected by the investigated time point, yielding a significant time of day effect ($p < .05$). Data inspection revealed that while performances remained fairly stable throughout the protocol in the elderly, young adults were able to even increase performance, particularly in the evening session after SD ($p < .05$). The results are in line with prior studies showing that procedural skill learning is possible with advanced age, even though it seems to be attenuated. Overall motor slowing in the elderly may have contributed to this disadvantage. Finally, although the interaction between session and age was not significant, our data point into the direction of an age-related attenuation of circadian and homeostatic modulations on procedural memory (significant main effect of session in the young, but not in the elderly).

G48 Auditory sensory gating responses in adolescents with a high genetic risk for schizophrenia

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Auditory sensory gating is expressed in the EEG as a response attenuation of the evoked response amplitude to the second click sound in a paired click paradigm. This gating was proposed as an endophenotypic marker for schizophrenia. Here, we investigated auditory sensory gating responses as well as Auditory Evoked Potentials in a group of adolescents with 22q11 deletion syndrome who have a high genetic risk of developing schizophrenia in adulthood. We investigated 15 adolescents with 22q11DS in a standardized paired-click paradigm and 12 matched controls with 120 binaurally presented paired-clicks (500 ms interval) with 256 channel EEG. We did not find any statistical differences between the two groups in amplitude reduction between the first and second P50, indicating that sensory gating was present in both groups. When investigating the amplitude over all channels with randomised tests, no differences between groups were found for each P50 component. In contrast, a distinct component was found in the 22q11 DS group at a latency of 90 ms that was not observed in the controls. Furthermore, the amplitude to the N100 was significantly reduced in the 22q11 DS group. If corroborated by further studies, this could point to different auditory processes leading to a reduced N100 component and thus a possible endophenotypic marker, while the pre-attentive processing around the P 50 might remain intact in a group that is at high risk for the development of schizophrenia.

G49 Inter-individual differences in circadian rhythmicity: effects of age and PER3 polymorphism

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Recent data provide evidence for a role of clock genes in sleep homeostasis. A variable number tandem repeat (VNTR) polymorphism in the human PER3 gene affects key markers of homeostatic sleep regulation and cognitive performance. Since aging is also associated with marked changes in sleep-wake patterns, we investigated how the PER3 polymorphism impacts on rest-activity cycles in young and older participants. Healthy older (age 55-75) and young (age 20-35) volunteers were selected only on the basis of their PER3 genotype (PER35/5, PER34/4 and PER34/5 participants). So far, subjective assessment of sleep and chronotype were conducted through questionnaires in 106 young and 63 aged subjects. 16 young and 26 aged homozygous volunteers were then included in a 3-week field study, in which they completed daily sleep diaries and continuously wore actigraphs.

Preliminary results confirmed a shift toward morningness with aging, as assessed by two chronotype questionnaires (MCTQ and MEQ; all $p < 0.0001$). However, the previously reported weak association of the PER3 polymorphism with morningness-eveningness was not confirmed. Actimetry data showed an age-related modulation in the activity profile, such that onset of the most active 10 hours and the 5 least active hours was advanced in the elderly as compared to the young (all $p < 0.005$). Moreover, data inspection revealed an effect of age ($F = 7.99$ $p < 0.0001$) and of PER3 polymorphism ($F = 1.32$ $p < 0.05$) on activity throughout the day. Most significant differences between aged and young were shown between 8-12am and 9-12pm. Significant differences in activity between genotypes were selectively found in the elderly, such that, as compared to PER34/4, PER35/5 individuals were more active between 6.5-8 am. In conclusion, our data confirm a phase advance in rest-activity cycles when getting older. Importantly, they also show that these rest-activity cycles are modulated by the PER3 polymorphism in the elderly but not in the young.

G50 Differences in anxiety/impulsivity and prefrontal cortex connectivity in the Roman High(RHA) and Low-(RLA) Avoidance rats

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Background: Adult animals of the two psychogenetically-selected Roman High-(RHA) and Low-(RLA) Avoidance rat lines differ in their coping style and vulnerability to stress. To see whether these differences are also present at earlier stages of development, we assessed behavioral performance in these two lines at distinct stages of development and correlated these observations to the morphological maturation of the medial prefrontal cortex.

Methods: RHA and RLA rats were tested in the Dark/Light Open Field (DLOF) test; latency to the first dark/light transition, time spent in light field and latency to start self-grooming were measured on postnatal days (PND) 20, 30 and 90. At these same time points, we used post-hoc iontophoretic Lucifer yellow cell labeling techniques to analyze dendritic arbor and spine density in layer 2-3 pyramidal neurons of the medial prefrontal cortex. Interneuron markers (parvalbumin, calbindin and calretinin) were used to quantify regional inhibitory network activity.

Results: At PND 20 no differences between the two strains were found for any of the behavioral or morphological parameters tested, except for the latency to start self-grooming, which is known to have a strong genetic component. At PND 30, however, RLA rats had an increased latency for the first dark/light transition and spent less time in the light field compared to RHA rats, both parameters being a measure of impulsiveness or inhibition/anxiety, and depending on prefrontal cortex function. We found a correlated increase in spine density of layer 2-3 pyramidal neurons and parvalbumin staining in the RLA compared to the RHA line at the same age, and this difference persisted up to PND 90.

Conclusion: The two rat lines differ already early at PND 20 in latency for self-grooming, a measure of emotionality. However differences in inhibition/anxiety or impulsivity, and the corresponding network changes in the prefrontal cortex are acquired later during the juvenile period and may result from a complex gene-environment interaction.

G51 Probing the involvement of both hemispheres during early stages of word processing by event-related TMS

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The present study exploits the decussation of the visual pathways to assess left and right hemispheric language function. Based on previous EEG results using a bilateral lexical decision task, we performed a TMS experiment with the same task to investigate the contribution of the left and right temporoparietal junctions during early stages of word processing. Two letter strings were briefly shown on each side of a central fixation cross, in the left (LVF), and right visual field (RVF). The stimuli were either a real word (neutral or emotional) or a pronounceable pseudo-word. Eight male volunteers were asked to press a button indicating on which side they had perceived a word. With a delay of 40 ms post-stimulus, a train of three TMS pulses (at 20Hz) was released over the target region. TMS over left and right temporoparietal junctions were compared to an active control stimulation over the vertex. Analysis of reaction times shows a slowing that is more pronounced when words are emotional and presented in the LVF after control normalized TMS to left or right temporoparietal junctions. This indicates that interference with both left and right temporoparietal junctions results in impaired processing of words that were presented to the left visual field. In addition this points to a specific contribution of the right hemisphere in the processing of words with emotional content compared to neutral words at very early stages.

G52 Influence of odor in aversive conditioning: assessing affective preparedness in the olfactory system

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Odor elicited emotions partly depend on their chemical structures, but also on learned associations or values, and it still remains debated whether some odors could be intrinsically pleasant or unpleasant. The present study aims at investigating whether different categories of odors could possess a dimension of affective preparedness, as previously shown for the visual and auditory sensory modalities. Preparedness can be assessed by aversive conditioning, and is reflected either by a faster acquisition or a slower extinction of the conditioned response. Two experimental groups (n=13 and n=14) underwent aversive conditioning by pairing odors with 2 sets of faces, expressing either a low or a high intensity of anger. An odor (pleasant or unpleasant, strongly or weakly trigeminal) was presented as a context during the 3 phases of conditioning (baseline; acquisition; extinction). After each trial, participants were asked to rate the level of anger expressed by the face, as well as the pleasantness, familiarity, intensity and subjective feelings elicited by the olfactory stimulation. Pupillary response to light, skin conductance, heart and respiratory rate were simultaneously recorded during the session. Preliminary behavioral results tend to show a different rating pattern according to the pleasantness of the context odor, which might reflect a difference in the conditioning process and in the preparedness dimension. The results obtained may provide a new paradigm to test for emotional preparedness in olfactory stimuli, and gain new insights about factors that influence olfactory-mediated attention.

G53 A novel, time-based non-matching to place protocol reveals short-term spatial memory deficits in monocarboxylate transporter MCT2 knockdown mice

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In an attempt to assess the role of MCT2 in short-term memory, we designed a non-matching to place task on an 8-arm radial maze requiring the animals to focus on the discrimination of more recently vs remotely visited arms (working memory). Briefly, mice introduced in the central platform of the radial arm maze had first access to only three baited arms. Once these arms visited, three more, intermingled arms were made accessible. Dependent variable was the number of entries in already visited arms (working memory errors). After 2 minutes of confinement in the center of the maze, a second trial started, where all baited, accessible arms were orthogonal to those of the first trial, thus introducing conflicting information as compared to the spatial references learned in the first trial. When administered to mice carrying human familial Alzheimer's disease transgenes, this test effectively discriminated carrier vs non carrier animals. The test was then administered to mice injected intrahippocampally with a lentivirus expressing a siRNA directed against MCT2 (MCT2 knockdown or KD mice). MCT2 KD mice were severely impaired in their ability to remember already visited arms (spatial working memory), as well as in the ability to benefit of recently acquired elements of salience, showing little or no improvement in working memory between the two consecutive daily trials. These results strongly support the role of MCT2 in mechanisms of sustained attention that might in turn result in memory deficits on a longer term scale.

H. System Neuroscience and Neuroinformatics

H1 Correlative microscopy of densely labeled projection neurons using neural tracers

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Three-dimensional morphological information about neural microcircuits is of high interest in neuroscience, but acquiring this information remains challenging. A promising new correlative technique for brain imaging is array tomography (Micheva and Smith, 2007), in which series of ultrathin brain sections are treated with fluorescent antibodies against neurotransmitters and synaptic proteins. Treated sections are repeatedly imaged in the fluorescence light microscope (FLM) and then in the electron microscope (EM). We explore a similar correlative imaging technique in which we differentially label distinct populations of projection neurons, the key routers of electrical signals in the brain. In songbirds, projection neurons can easily be labeled using neural tracers, because the vocal control areas are segregated into separate nuclei. We inject tracers into areas afferent and efferent to the main premotor area for vocal production, HVC, to retrogradely and anterogradely label different classes of projection neurons. We optimize tissue preparation protocols to achieve high fluorescence contrast in the FLM and good ultrastructure in the EM (using osmium tetroxide). Surprisingly, we observe that fluorescence can still be detected in ultrathin sections of osmicated tissue, especially in subcellular compartments where fluorescence was strong prior to EM preparation. In order to recover signal of tracer in areas where fluorescence is not directly detectable, we label the tissue with fluorescent antibodies against the tracers. The signal can be detected in fine neural processes close to synapses, allowing for their classification as belonging to a specific population of projection neurons. The use of our method will be to provide statistical information about connectivity among different neuron classes, and to elucidate how signals in the brain are processed and routed among different areas.

H2 Dopamine innervation of Area 10 of prefrontal cortex in normal and MPTP treated macaques

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Dopamine (DA) is a central neuromodulator whose release in the neocortex has a strong influence on cognitive functions, such as reward learning and attention. In area 10 of the prefrontal cortex of two macaque monkey brains, we used antibodies directed against tyrosine hydroxylase (TH), the synthetic enzyme for DA, to identify DA-containing boutons. The DA boutons were large and contained many vesicles, but rarely formed conventional synapses. The simplest explanation is that DA acts by non-synaptic release and diffuses to receptors in the surrounding neuropil. We thus extended our study to analyze quantitatively the neuropil in the immediate vicinity of the DA boutons and found that they had a higher proportion of their perimeters in contact with dendritic shafts and unlabeled boutons and significantly less contact with dendritic spines. Interestingly, DA boutons were also significantly more often in continuous contact with a pair of pre- and postsynaptic structures. These differences indicate that DA boutons might influence the perisynaptic regions by 'broadcasting' their signal, rather than by acting over the restricted spatial range of a conventional synapse. MPTP treatment selectively destroys DA neurons in the midbrain. In two MPTP treated monkeys, the DA innervation of area 10 was far sparser than controls, axons were thinner, and the boutons were shrunk. All these are consistent with degenerative changes caused by loss of midbrain DA neurons, which lead to Parkinson's disease.

H3 Local excitatory circuits of macaque Area 8A (Frontal Eye Fields)

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Do all local circuits of neocortex follow common design principles? As a 'proof of principle' test we showed by simulation that a biologically-detailed circuit derived from cat area 17 could fulfil the computational demands of a prefrontal cortical area, Frontal Eye Fields (FEF) in monkey and man (Heinzle et al., 2007, 2010). FEF controls saccadic eye movements in macaque monkey and most likely the eye-movement for reading in man, as well as providing an attentional signal for areas like V4 (Moore and Armstrong, 2007). Our spike-based model of FEF made specific predictions about the structure of the circuit, which we have begun to test. Small clusters of neurons were labelled by ionophoretic injections of biotinylated dextrine amine (BDA) into different layers of FEF in 3 monkeys. LM reconstructions of pyramidal cells in layers 2 and 3 showed the typical axonal branching pattern seen in the cat: clustered collaterals around the dendritic tree, extensive lateral directed axons forming clusters up to 4mm distant from the soma within the superficial layers, and a descending axon arborising in layer 5. Electron microscopic analysis of the synaptic targets of the local axon indicates that, as in the cat, the major targets (78%) were the spines of other pyramidal cells. The remaining synapses were formed with shafts of smooth neurons. These observations support the 'canonical circuit' hypothesis that common principles are at work in constructing neocortical circuits.

Acknowledgements: European Union; daisy grant number FP6-2005-015803 (HK and KACM) and SNF, NCCR grant:

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H4 Dissecting the role of interneuron subtypes in fear learning: an optogenetic approach.

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The amygdala is a key brain structure for learning and extinction of conditioned fear. These two processes are not only important model paradigms for investigating the neuronal basis of learning and memory, but are also of high clinical relevance for human anxiety disorders. Up to now, research on the neuronal substrates of fear conditioning and extinction has mostly focused on the excitatory network elements. The role of inhibitory interneurons in the amygdala is, however, poorly understood. Based on knowledge from other brain areas like the hippocampus, it is conceivable that different interneuron classes, defined by molecular markers, morphology and connectivity, fulfill distinct functions in the network. Roles in fear extinction or generalization have been suggested. However, determination of these functions was hindered by the lack of appropriate techniques. Optogenetics allows now to overcome this limitation and may provide causal relationships between neuronal activity and behavior. We are applying a cell-type specific optogenetic approach, based on conditional AAVs and interneuron-specific CRE mouse lines, in combination with single unit recordings in behaving animals to investigate the physiological functions of different interneuron subclasses in the amygdala. Experiments in a PV+ CRE line showed significant, differential effects on fear learning, depending on the exact timing of PV+ interneuron activation. Physiological activity during fear learning could also be monitored in single unit recordings of optogenetically identified PV+ interneurons. In the future we hope to understand the distinct roles of the different interneuron subclasses by bidirectional optogenetic manipulation of neuronal activity during different phases of fear behavior, like fear expression, generalization or extinction. Thereby we hope not only to further understand the basic mechanisms of fear learning, but also to uncover general principles of neuronal circuit activity and plasticity during learning and memory.

H5 Optogenetic analysis of activity pattern readout in the zebrafish homolog of olfactory cortex

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Neuronal circuits in the olfactory bulb transform distributed spatial patterns of activation across the input channels, the glomeruli, into spatio-temporal patterns of activity across the output neurons, the mitral cells, that are conveyed to multiple higher brain areas. During an odor response, stimulus-specific subsets of mitral cells rhythmically synchronize their action potentials with millisecond precision, while responses of the majority of mitral cells show no obvious synchrony. Since synchronized and non-synchronized action potentials convey information about complementary stimulus features, it is important to determine whether higher olfactory brain areas are sensitive to synchronized input, as found in insects. We addressed this question in telencephalic area Dp of zebrafish, which is homologous to olfactory cortex in mammals. Using a digital micromirror device (DMD) and transgenic fish lines expressing channelrhodopsin-2 (Chr2) in the olfactory bulb, we optically imposed spatiotemporal activity patterns onto the population of mitral cells with high precision. Whole cell recordings confirmed that mitral cell responses depended on the spatial pattern of light stimulation and became more synchronous as the synchrony in the activation pattern was increased. We then performed whole-cell recordings from Dp neurons to explore how their responses depend on the oscillatory synchrony of mitral cell input. Synchronous mitral cell activity was detectable in the membrane potential fluctuations of Dp neurons. However, oscillatory fluctuations were small and did not contribute substantially to the depolarization underlying suprathreshold odor responses, indicating that they are filtered out. These results indicate that Dp neurons maximize the impact of non-synchronized input, which is particularly informative about precise odor identity.

H6 Canonical circuits in mouse auditory cortex

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The mammalian neocortex is divided in different areas based on their cytoarchitectonic properties and functional specification. Our hypothesis is that despite their different functional roles, these different cortical areas have a similar local circuit that we refer to as "canonical circuit". Presently the only cortical area for which there is a comprehensive quantitative description of the connection matrix is the cat visual cortex. The aim of this work is to obtain a comparative description of the mouse auditory cortex (A1). In order to obtain such a connection matrix a fine detail description of the axonal and dendritic arbors of A1 neurons is essential.

We labeled the mouse A1 neurons in vivo with intracellular injections of horseradish peroxidase (HRP), and reconstructed their morphology in 3-D. The layer location of the soma was based on their distance from the pia and after comparison with Nissl staining and osmicated sections. Neurons (n=10) from layers 2 to 6 were filled. In layer 4 neurons (n = 6), all neurons were pyramidal in morphology and most of the axonal branches showed lateral projections confined to layer 4, without forming the axonal clusters typically seen in cat layer 4. The remaining branches projected towards the surface of the cortex, including layer 1. Our results show that in the mouse like in the cat, there is a strong recurrence of the connections within layer 4 neurons. In the cat, this strong recurrence is thought to play a role in the amplification of a weak thalamic input. We propose that a similar function is performed in layer 4 of mouse auditory and that the strong recurrence of layer 4 is one of the canonical properties of the cortical microcircuit.

H7 Encoding odors by spike packets sequences from ensemble of rate-invariant neurons in awake mice

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How do neural networks encode sensory information? Following sensory stimulation, neural coding is commonly assumed to be based on neurons changing their firing rate. In contrast, theoretical works showed that neurons, simply by adjusting their spike timing and without changing their firing rate, could encode information as coordinated cell assemblies. Nevertheless, experimental evidences supporting such model remain weak. Here we show, in awake mice, that following odor presentation a large fraction of olfactory bulb output neurons do not significantly change their firing rate but were found to respond by redistribution of their firing activity within respiratory cycles. In addition, we showed that sensory information can be encoded by cell assemblies composed of such neurons, thus supporting the idea that coordinated populations of rate-invariant neurons could be efficiently used to convey information. Finally, we showed that different codes could be used to convey high amount of odorant information but only for specific read-out time window. We propose that odorant information may be decoded by downstream network as sequence of spike packets of gamma oscillation duration, in order to reach a tradeoff between rapid and accurate odor discrimination.

H8 Dense sensory input maps evoked by natural odorants in awake mice

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In mammals, odorant molecules are sensed by a large family of olfactory receptor proteins expressed by sensory neurons in the nasal epithelium. These neurons select only one receptor out of a large possible repertoire (1000 genes in mouse) and their axons converge in a receptor specific manner onto segregated anatomical structures called glomeruli in the first brain relay of olfaction, the olfactory bulb. Functionally, odorants evoke combinatorial patterns of activated glomeruli, representing the first basis of odor coding. In the past years, several studies showed that simple or complex odors activate only a very limited subset of the total glomeruli number, leading to a theory of sparse odor coding. Although this idea has largely spread out, it does not make a general consensus as conclusions were drawn from experiments done in anesthetized animals and further biased by the arbitrary use of only limited ranges of odor concentrations. In this study, we imaged odor evoked patterns in awake mice using intrinsic signal imaging and two photon microscopy. We used a large panel of natural odors for which we don't have to worry about ethological relevance of the concentration. Our results show that all the odorants tested activated a large number of glomeruli, representing between 5 to 25% of the entire population. We therefore conclude that natural odorants evoke dense representations in the olfactory bulb, suggesting that odor coding theories in the olfactory system may have to be revisited.

H9 Temporal dynamics of spiking and LFP activity depend on CRT monitor refresh rate in tree shrew primary visual cortex

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Tree shrews are day active mammals with a well developed visual system, and are close relatives of primates. Here we characterize neural responses in the primary visual cortex (V1) of the anesthetized tree shrew to sparse noise stimuli presented on a cathode ray tube (CRT) video monitor. We recorded spiking activity and local field potentials in 52 single and multi units in different V1 layers using tetrodes at monitor refresh rates of 60, 90 and 120 Hz. We find strong entrainment of spiking and LFP responses to the monitor refresh rate. This effect is most pronounced in the input layers of cortex and at low refresh rates. Moreover we find refresh rate dependent differences in response latencies, temporal response profiles as well as in black/white preference of cells. Our data show that a wide range of neuronal response characteristics is influenced by the refresh rate of the stimulating monitor. These effects are important to consider for experimental design and data interpretation.

H10 Reconstruction of neuronal connectivity in the zebrafish olfactory bulb by 3D electron microscopy

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The olfactory bulb (OB) of zebrafish is a model to study the processing of neuronal activity patterns by circuits of interconnected neurons. Odors evoke coarsely topographic, distributed patterns of activity across the input modules of the OB, the glomeruli, already in larvae. Glomerular activity patterns are then reorganized by inhibitory interactions within the OB, resulting in normalized and decorrelated activity patterns across the output neurons, the mitral cells. In order to understand the mechanisms underlying these computations, it is essential to analyze the connectivity between neurons in the circuit. Classical anatomical methods can reveal only connectivity between small numbers of neurons and generate first-order statistical information. We are therefore exploring 3-D electron microscopy to determine exhaustive connectivity matrices by complete ultrastructural imaging of large tissue volumes. Using serial block face scanning electron microscopy, we obtained stacks of EM images from the OB of zebrafish larvae at a section thickness of 30 nm. Staining procedures used allow for the visualization of neuronal morphology and intracellular organelles including synapses. Subsets of neurons were reconstructed manually using different approaches. This approach has the potential to reconstruct near-complete wiring diagrams of neuronal circuits in the developing OB and other brain areas.

H11 Layer-specific cholinergic modulation in the tree shrew primary visual cortex

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Acetylcholine (ACh) plays a pivotal role in a multitude of cognitive functions, brought about by a mixture of positive and negative modulation depending on nicotinic and muscarinic cholinergic receptors. To ascertain better the effects of ACh on cortical processing, we investigated the influence of iontophoretic application of a nicotinic and a muscarinic cholinergic receptor agonist on neural responses in different layers of V1. The location of recording sites was verified by making electrolytic lesions and reconstructing their location using cytochrome oxidase immunohistochemistry. We recorded single neuron activity from 139 neurons in 8 anesthetized tree shrews during visual stimulation using drifting sinusoidal grating stimuli of various contrasts. We found strong layer-dependence of nicotinic effects on the contrast response of V1 neurons, with largest effects observed in the granular input layer, where thalamic signals enter the cortex. By contrast, muscarinic activation had weak effects on neural contrast sensitivity across cortical layers. Examining the orientation tuning of these neurons, we found that muscarinic activation enhanced orientation sensitivity in supra- and infragranular layers, with relatively weak effects in the granular layer. Nicotine had less pronounced effects on orientation sensitivity. Our results suggest cholinergic modulation affects specific layers and visual feature representations through mechanisms that are specific to its two main receptor types. Our findings extend previous work in monkeys, and suggest close homology between cholinergic modulation effects on visual function in monkey and tree shrew visual cortex.

H12 Measurements and learning experiments in a neuromorphic VLSI system.

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We propose to study the computational properties of neural systems by building large-scale brain-inspired artificial neural networks and real-time sensory motor systems using hybrid analog/digital VLSI circuits. We focus on neuron and synapse circuits that exploit the physics of silicon to reproduce the biophysics of neural systems (for example we exploit the diffusion of electrons across a transistor channel to directly emulate the diffusion of ions across a proteic channel).

In order to achieve this equivalence, it is necessary to map biophysical parameters to circuit parameters. As a first step, to characterize the hardware neurons and synapses we designed, we measured systematically their response properties as a function of their parameters. We show results obtained from a single VLSI silicon synapse characterizing the circuit's time constant and synaptic efficacy. We also demonstrate the behaviour of the silicon neurons by measuring their input-output firing rate relationship. The VLSI circuits are integrated on a prototype chip, comprising 128 neurons and 4096 synapses. As the circuit are affected by device mismatch, the silicon synapses and neurons are inhomogeneous (even though they were designed to be identical). The results we present include the characterization of the mismatch effect.

To account for such non-idealities at the system level, and use these devices in neural network applications, we have to resort to the same strategies that the real nervous system uses: adaptation and learning. Therefore we present also preliminary results on a spike-based learning model that is also implemented in VLSI, on the same prototype chip.

H13 Retinal and post-retinal contributions to the Quantum efficiency of the human eye.

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The retina is one of the best known quantum detectors with rod photoreceptors being able to elicit neural signals for a single incident photon in animal experiments. This has led to the proposal of using humans as detectors for quantum phenomena such as entanglement. However, these experiments would require accurate and reproducible detectors and would be based on the reports of the subjects about whether or not a few photons are able to elicit conscious perception. Estimates on the number of photons needed for conscious perception, based on signal detection theory, are systematically above the estimates obtained in animals and the reasons for this discrepancy remain poorly understood. One possibility is that post-retinal processing significantly contributes to the decrease in the quantum efficiency determined by signal detection theory and adds noise to the detection process. To shed light on this issue we carried out experiments in dark-adapted humans using well controlled sources of light while recording EEG signals and behavioral parameters such as reaction times. Exactly half of the participants behaved as noisy detectors reporting perception in trials where no light was sent. Noisy subjects were significantly faster than the others to take decisions but equally accurate in terms of detection thresholds. Reaction times significantly increased with the decrease in the number of incident photons. This trend was clearly reflected in the latency and onset of the mean EEG responses over frontal and parietal contacts where the first significant differences in latency were detected. Delays in latency of neural responses across intensities were observed later over visual areas suggesting that they are due to the time required to reach the decision threshold in decision areas rather than to longer integration times at sensory areas inherited from retinal contributions. As a whole our results suggest that post-retinal processing significantly contribute to increase detection noise and detection thresholds, decreasing the quantum efficiency of the whole detector (retina+brain) with respect to the efficiency of the retina alone.

H14 How the brain ultrastructure is altered by conventional EM preparation techniques

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The aim of this study is to understand the extent to which conventional electron microscopy preparation techniques distort the arrangement of synapses, neurites, and astrocytic processes in the adult mammalian cortex. With recent advances in large volume 3D EM imaging techniques, detailed analysis of tissue volumes is becoming more commonplace. However, despite many functional studies showing that about a fifth of the brain tissue is composed of extracellular space (ECS), this is ignored in most ultrastructural studies. A rare exception is the work of Van Harreveld and colleagues (*) in the early seventies that tried to overcome these problems. In this study we have used in vivo imaging techniques, the latest cryopreservation technology, and 3D electron microscopy. After conventional perfusion fixation, we show that the cerebral cortex of the adult mouse shrinks by up to 30% in volume, with an almost complete removal of the ECS. Concomitant with this rearrangement is a modification to the volumes occupied by the axons, dendrites and astrocytes; and a proportional increase in the density of synaptic contacts. These results highlight the care that needs to be taken in interpreting the functional interactions between different cellular elements in the CNS based solely on conventionally prepared tissue.

*Van Harreveld and Malhotra, J. Anat. (1967), 101, 2, pp. 197-207

This work is supported by the Stoicescu Foundation, Swiss National Science Foundation and Human Frontier in Science Program.

I. Brain Imaging

I1 Impairment of prefrontal activation and connectivity during executive function in Parkinson's Disease: a combined fMRI/DTI study.

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Purpose: Executive deficits in Parkinson's Disease (PD) may have a significant impact on the quality of life of these patients. Previous studies suggest that executive function depends not only on the prefrontal cortex (PFC) but also on intact frontostriatal connectivity mediated by dopaminergic neurotransmission. Thus, the working hypothesis is that abnormalities in the cognitive fronto-striatal loop will affect executive processing in PD patients. To investigate the performance and brain activation during executive processes and the relation between functional activation (fMRI) and structural connectivity (DTI) of the frontal cortex in PD subjects, we designed a study using fMRI and DTI probabilistic tractography. **Methods:** In the fMRI part of this study we used an established verbal WM task, which is known to activate dorsal- and ventro-lateral prefrontal areas (DLPFC, VLPFC), to delineate activation related to working memory processes in 8 idiopathic PD patients and healthy aged matched control subjects. The obtained fMRI activation maps were then used to determine seed regions for probabilistic tractography analysis. To investigate connectivity patterns of the DLPFC and VLPFC regions known to be involved in WM processes, seedmasks of these areas were drawn and consequently used for a DTI connectivity analysis using probabilistic tractography. **Results:** In PD, our fMRI results demonstrated an impaired activation in the left VLPFC, left and right DLPFC, the right anterior cingulate, and the left caudate as compared to healthy subjects (HS). The subsequent connectivity analysis of the dorsal (DLPFC BA9 & BA9/46) and ventral prefrontal areas (VLPFC BA45 & BA47) demonstrated significantly weaker connections in PD (compared to HS) with the dorsal caudate nucleus and several other cortical areas. **Conclusions:** This study provided evidence for reduced cortico-cortical and corticostriatal connectivity in association with working memory processes in PD. Despite the fact that dopaminergic degeneration of the SNc is the prerequisite for the diagnosis of PD (Jankovic, 2008), clinical outcome can vary considerably (Lewis et al., 2004). The combined functional and structural investigations may help in dissecting and correlating neural correlate with clinical subtypes of PD.

Support: FRSQ grant to AP, postdoctoral fellowship from FRSQ to SEL

I2 Localisation of epileptic generators with EEG-fMRI informed by EEG topographic maps

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Background: In patients with medically refractory focal epilepsy who are candidates for epilepsy surgery, concordant findings from non-invasive multimodal imaging are needed to localise the epileptic focus and guide intracranial EEG recording and/or resective surgery. Simultaneous EEG-fMRI can map focal haemodynamic (BOLD signal) changes related to interictal epileptiform discharges (IED) detected on the EEG and is a useful tool to localise the epileptic focus. However, EEG-fMRI studies are negative in 40-70% of cases due to a lack of IED or absence of significant correlated BOLD changes. Here, we aimed to use EEG topographic features of the epileptic activity derived from long term clinical EEG monitoring (LTM) to inform EEG-fMRI analysis. **Methods:** After building the topographic map of averaged IEDs recorded during LTM, we calculated the timecourse of the correlation of this map with the intra-MR EEG topography. This timecourse was used as a regressor for fMRI analysis in a General Linear Model (GLM). Results were validated with intracranial recordings or resection zone in post-operatively seizure free patients. Concordance was labelled as good, when the maximal statistical BOLD change ($p < 0.001$ uncorrected) or of any corrected BOLD change (family-wise error correction $p < 0.05$) was located < 15 mm from seizure onset zone on intracranial EEG or from resection area on post-operative imaging. Concordance was labelled as moderate when a non-maximal uncorrected BOLD change was spatially congruent with intracranial EEG or post-operative imaging with the same criteria. **Results:** In 5/5 patients with IED-related BOLD signal change on conventional analysis, that were concordant with the seizure onset zone, the topographic analysis gave similar concordant results. In 14/18 (78%) patients with absent BOLD changes following conventional analysis, the topographic method showed good concordance ($N=9$) or moderate concordance ($N=5$) with intracranial EEG or resection area in post-operative seizure-free patients. **Discussion:** We showed that pathological EEG topographic features have haemodynamic correlates and that our method dramatically increases the yield of EEG-fMRI. These findings could have important implication in the presurgical evaluation of patients with epilepsy.

I3 Sodium imaging: new strategies for optical probing of neural circuits.

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Changes in intracellular sodium concentration ($[Na^+]_i$) underlie many important cellular processes from action potential generation to neuron-astrocyte metabolic coupling. Nonetheless, measuring $[Na^+]_i$ with fluorescent probes have proven more difficult than measuring Ca^{2+} changes. This is due to the relatively small amplitude of $[Na^+]_i$ responses during physiological processes as well as to the suboptimal characteristics of available fluorescent probes. Most studies so far relied on sodium-binding benzofuran isophthalate (SBFI). We undertook several approaches in order to provide new tools for detecting sodium in living preparations. The first approach was to implement single-cell electroporation of SBFI in astrocytes in brain slices. This method resulted in an improved signal to noise ratio as compared with bulk loading the AM form of the dye while avoiding the run-down of cellular metabolites that often happen when delivering the dye through a patch pipette. We then turned our efforts to finding sodium dyes excitable in the visible spectrum to avoid the disadvantages of UV illumination required when imaging SBFI. The second approach was thus to modify an existing visible-spectrum sodium organic dye CoroNa Green by coupling it to dendrimers in order to avoid its rapid leakage from cells. This strategy proved successful in retaining CoroNa Green in the cytosol and allowed us to accurately measure neuronal and astrocytic signals in situ over long durations. Last approach consisted in testing new synthetic dyes in order to identify a candidate that would have all desired specifications. Asante Natrium Green appeared to fulfill our requirements. This new sodium indicator could be excited both in the visible spectrum and with two-photon illumination, showed a stable and homogenous cytosolic loading, responded specifically to changes in $[Na^+]_i$ with a useful dynamic range, did not display any significant photobleaching or phototoxicity. We successfully used it to characterize physiological neuronal and astrocytic responses. Altogether, these new tools make it now possible to use sodium imaging to probe neural circuit functions in situ.

I4 Functional mapping of cortical language areas with functional MRI in individual subjects

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In the last two decades, several tasks for fMRI-based non-invasive mapping of brain language areas for presurgical evaluation have been proposed. However, while hemispheric lateralization of language has become reliable and concordant with invasive procedures in clinical populations, reliable individual localization of crucial language areas within the dominant hemisphere still remains challenging. Here, we present the data of 22 right-handed, healthy subjects who performed an auditory semantic decision task including congruent, incongruent and non-sense short sentences (Astesano et al., 2004) in an fMRI event-related design. The group analysis revealed activations in the left superior temporal and left inferior frontal gyri corresponding to Wernicke and Broca's areas, respectively. Moreover, these areas were also activated in most of the individual subjects. We conclude that this semantic decision task is a promising paradigm for robust localization of crucial language areas in individual subjects. The short duration and the simplicity make it particularly suitable for patients with cognitive impairments. Reference: Astesano C, Besson M, Alter K. Cogn Brain Res. 2004.

I5 Error processing and post error adjustment in a flanker task

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The ability to detect errors and adjust behavior accordingly is essential for maneuvering in an uncertain environment. The brain correlates of post error adjustments that occur in executive control tasks are poorly known. We recorded 32 subjects performing a modified flanker task in a 3T magnet. As expected the behavioral results showed a significant incongruity effect ($F = 27.689, p < 0.001$) and a strong post error slowing ($t = 2.97, p = 0.006$). Those behavioral results were concomitant with activation of a conflict network including anterior cingulate cortex (ACC), anterior insula, and lateral prefrontal cortex (LPFC). In addition, an error detection network including the same regions (ACC and insula) was more activated, but additionally accompanied by specific dorsal striatal activations. Finally, we observed an increase in a bilateral attentional network including parietal cortex and LPFC for the post error trials. Conversely, post error trials disengaged ventral striatum. Those results support recent findings that frontal cortical areas play distinct executive roles in behavioral adjustments: the ACC acts retroactively to enable behavioral adaptation whereas the LPFC reconfigures cognitive processes constituting the adjustment. Furthermore, we found a striatal involvement in the post error adjustments. This new finding in fMRI investigations support the striatum mediates cortical signals to achieve behavioral adjustments. We conclude that adaptation of behavior requires a fine-tuned recruitment of the frontal cortical-basal ganglia neural network.

I6 Human Primary Auditory Cortex Follows the Shape of Heschl's Gyrus

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Introduction: Over 100 years ago human primary auditory cortex (PAC, Brodman's Area 41) was first identified in post-mortem tissue based on its dense cellular structure and myelination. Today, the borders of PAC are still not routinely identifiable in the living human brain. PAC can be identified functionally based on its topographic mapping of preferred sound frequencies (known as tonotopy or cochleotopy), but human tonotopic maps have been challenging to measure, thus far, because of their small size relative to the spatial resolution of standard non-invasive neuroimaging techniques.

Methods: Here, using ultra-high field strength fMRI at 7 Tesla, we measured auditory tonotopic maps relative to the underlying anatomy of Heschl's gyrus (HG) in 10 human subjects. We provide the clearest measures of human tonotopy to-date. Anatomical variants of the HG are known to be common (including partial and complete duplications of the gyrus) and we specifically considered the range of variants.

Results: In all subjects we measured the two primary mirror-symmetric tonotopic maps (high-to-low-low-to-high). In 20/20 hemispheres, map iso-frequency lines clearly ran parallel to the long-axis of HG, thus settling a long-standing debate about the orientation of the maps. In cases of partial or complete gyral duplications (11/20 cases), primary auditory cortex spanned both divisions of HG not only the anterior part as previously assumed. Furthermore, the representation of low frequencies (the union of the two mirror-symmetric tonotopic maps, the border between primary subfields A1 and R) was centered on HG and co-localized with the dividing sulcus in the case of partial or complete HG duplications.

Conclusions: This precise structure-function relationship significantly refines HG as a marker for primary auditory cortex and indicates that several previous studies have mislocalized or underestimated the size of human PAC. Furthermore, the union of mirror-symmetric tonotopic maps on the crown of the gyrus suggests a striking a previously unknown organizational parallel with the visual cortex where the union of mirror-symmetric retinotopic maps (the V1/V2 border) also occurs on a gyrus.

I7 Hemispheric asymmetry of cortical terminations of the human arcuate fasciculus: an in vivo probabilistic tractography study

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In vivo diffusion imaging (i.e., DTI) studies provide a wealth of new information regarding the connective anatomy of the perisylvian network. It is acknowledged that the arcuate fasciculus has tract components besides the long segment and that these regions terminate in more remote areas. Our aim was to investigate the hemispheric asymmetry of this extended network.

40 right-handed adults were examined using DTI; imaging data were standardized to an MNI152 template. A probabilistic framework was used for tractography. The long segment was determined by searching for pathways connecting the frontal and temporal lobes then outlining it on the connectivity map. To reveal a more extended network, this area was re-used to initiate fibertracking. 14 perisylvian cortical regions were defined as terminations for tractography; this allowed to calculate the number of tracts that pass through the arcuate while terminating in a specific area, which putatively correlates with the strength of connection. Overall statistics and gender-related variations in connection strengths and lateralizations were determined. Overall leftward lateralization was found in projections to the superior temporal gyrus and the anterior division of the middle temporal and the supramarginal gyrus. Rightward lateralization was observed for the angular gyrus, posterior parts of the supramarginal gyrus and MTG. Similar patterns were revealed in both genders except for the more bilateral distribution of the frontal connections in females.

Our findings demonstrate a tractography approach for the basis of inter-hemispheric asymmetries. We report that different components of the perisylvian network are not exclusively lateralized left. By quantitatively describing the connective asymmetry we emphasize that the rightward lateralizations suggest a complex function of the contralateral perisylvian network, which requires further investigation.

I8 Content-specific memory reactivations depend on medial temporal lobe integrity

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In our previous work we found category-specific reactivations in word (VWFA) and face (FFA) specific areas, when subjects were implicitly retrieving a word or face in response to a memory cue. Because a large body of research suggests that the MTL is implicated in memory retrieval, in the present functional magnetic resonance (fMRI) study we investigate the role of the MTL in memory reactivations observed in cortical areas. By using an associative memory paradigm in patients who underwent partial MTL resection in the course of epilepsy treatment, we probe whether lesion side and/or memory content affect the reactivations in VWFA and FFA during cued retrieval in those patients. Our experiment comprises a learning phase in which participants study pairs of stimuli, followed by a test phase. Each pair consists of either a scene and a face, or a scene and a word. In the test phase we present scenes only (one in turn), and participants have to indicate whether this scene was previously paired with a face, a word, or is new. In a group of patients with left hemispheric lesions preliminary fMRI results for the test phase show intact reactivation for remembered face-associations in FFA, but not word-associations. A single patient with right hemispheric lesion showed intact reactivation for word-associations in VWFA, but not face-associations. For all patients the behavioural performance was above chance. These preliminary results indicate a relationship between MTL integrity and neocortical reactivation during memory retrieval.

I9 Speech in Noise: Neural substrates of challenging speech perception with and without supporting semantic context

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Nine listeners (3 male) took part in an fMRI investigation of the neural basis of auditory backward semantic priming. We systematically varied the semantic relatedness of primes and targets in a backward-masking paradigm and embedded the primes in varying levels of background noise. By examining the effects of these two variables we are able to isolate the cerebral networks that are implicated in processing speech in noise, as well as those implicated in making use of semantic context, in particular when speech is degraded. A significant main effect of signal to noise ratio (SNR) was observed in a network comprising the anterior insulae, left inferior frontal gyrus (the pars opercularis and pars triangularis), bilateral cuneus and precuneus, and bilateral middle orbitofrontal cortex. The insulae and left inferior frontal activations show increased activation in response to decreasing SNR, implying that they are more actively engaged under sub-optimal listening conditions. The more posterior regions and the middle orbitofrontal gyrus show greater deactivation in response to decreasing SNR. These regions form part of the resting-state network, and appear to be more suppressed during challenging conditions, possibly due to a 'limited capacity' allocation of resources to more actively engaged regions. A context-by-SNR interaction is found in the left angular gyrus, suggesting that this region may be involved in using semantic context to support the processing of challenging speech.

I10 Modulation of auditory spatial attention through emotion: an fMRI auditory dot-probe study

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Emotional stimuli can modulate attentional orienting through signals sent by cortical nuclei which modulate visual perception at early stages of processing. Very few studies aimed at investigating the influence of emotional stimuli on attentional orienting in the auditory domain. Thus, we used an auditory dot-probe paradigm involving simultaneously presented neutral and angry non-speech utterances (voices) each lateralized to one side of the auditory space. They were immediately followed by short and lateralized single sine wave tones presented on the side of the preceding angry voice (valid trial) or on the opposite side (invalid trial). Participants had to quickly indicate the side where the tone was presented. We supposed that angry compared to neutral voices attracted attention and facilitated processing of targets which matched the same side of presentation. Behavioral results showed the expected facilitation effect and functional imaging results showed an involvement of the right anterior/left mid STG for the decoding of angry emotional vocalizations, even if they were not related to the participant's task. Those regions partially overlap with results obtained in a functional voice localizer during the same fMRI session, and using the previously described voices (non-speech utterances). Eventually, a psycho-physiological interaction analysis revealed activity in the middle frontal gyrus, inferior parietal lobule and left and right STG associated with seed activity in the left STG region. Taken together, these results suggest an involvement of the STG regions not only for processing voice prosody, but also for orienting attention toward a target present in the auditory space, thus allowing for a fast detection when the source is cued by an emotionally implicit voice stimulus.

I11 Electrophysiological evidence for ventral stream deficits in schizophrenia

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Visual deficits in schizophrenic patients are often attributed to impairments in the dorsal ('where') stream of visual processing. Ventral ('what') stream impairments have not been as well investigated, but a better description of ventral stream impairments may be important to help understand the myriad cognitive impairments in schizophrenia, because vision precedes cognition. We used a visual masking paradigm in which patients, controls, and not-affected relatives discriminated small target offsets. We recorded EEG and applied distributed, linear EEG-source imaging techniques to reconstruct source differences of the evoked potentials throughout the brain. Compared to controls and relatives, patients showed strongly reduced discrimination accuracy. These behavioral deficits corresponded to pronounced decreases in evoked responses at around the N1 latency (200 ms). At this latency patients showed decreased activity that was most pronounced in the left fusiform gyrus. These electrophysiological results reveal large deficiencies in ventral stream processing of schizophrenic patients.

I12 Manipulating Visual Perception with Real-Time fMRI-based Neurofeedback Training

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Spontaneous fluctuations of ongoing brain activity have a profound impact on perception. For example, human observers are more likely to perceive a visual stimulus if baseline activation in visual cortex at the time of presentation is higher. Here, we used real-time fMRI-based neurofeedback to teach participants to voluntarily regulate the ongoing brain activation of circumscribed areas in their early visual cortex. We then tested how such self-regulated activation influenced subsequent processing of a visual stimulus presented near threshold. We found that the level of activation within early visual cortex directly influenced objective detection thresholds, i.e. when the participants increased activation they became better at detecting a visual stimulus. This improvement was specific to stimuli that were presented at a location overlapping with the self-regulated ROI, i.e. no improvements were found for other visual field positions. A control group who received feedback from a non-visual brain region did not learn to control visual cortex activation and did not show changes in visual sensitivity. Hence, with real-time fMRI-based neurofeedback it is possible to learn voluntary control over visual cortex activation and thereby to improve visual sensitivity. This new approach allows us to now use perception as a variable which is dependent on self-regulated brain activation, and therefore to investigate causal links between brain activation and perception.

I13 Neural face coding is shaped by race

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Human populations can be categorized by salient phenotypic traits, a visual process defining the social concept of race. Race markedly impairs one of the most critical and specialized skill humans possess: the recognition of conspecifics. Humans are significantly better at recognizing Same-Race (SR) than Other-Race (OR) faces, feeding the popular belief that OR faces all look alike. Theoretical (Valentine, 1991 – figure 1a) and computational (e.g., Caldara & Abdi, 2006 – figure 1b) Norm-Based Multidimensional Face-Space Models (NBMDFSM) have provided a consistent account for this universal Other-Race Effect (ORE). In NBMDFSM, efficient SR face identification is achieved by sparser coding across diagnostic dimensions for SR compared to OR face-exemplars, a by-product of visual experience. Neural evidence for NBMDFSM coding has been found with fMRI in humans and single-cell recordings in monkeys. Surprisingly, whether and where such neural face coding subserves the laws predicted by NBMDFSM of the ORE is unknown. We measured Western Caucasian (WC) and East Asian (EA) observers' BOLD signals in functionally defined face-selective Region of Interest (ROI – Fusiform Face Areas (FFA) and Occipital Face Areas) while they perceived normalized WC and EA faces (10 identities per race). We then computed Representational Dissimilarity Matrix (RDM – Kriegeskorte et al., 2008) in each ROI independently, by correlating the BOLD response elicited by each identity within a race with the remaining 9 across the multidimensional voxel population (figure 1c). We found significant higher RDM r-values for OR compared to SR faces in the FFA, relating to prototypical (less distinctive) activation patterns for OR faces in both groups of observers. We used RDM to link neural face representations with psychological and computational NBMDFSM of the ORE. This multidimensional voxel mapping quantified coding efficiency in the FFA for individual SR faces. This finding has profound implications for the understanding of the ORE and face perception.

I14 Electrical Neuroimaging of Early Sensory Processing in First-Episode Psychosis

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Low-level, early auditory and visual impairments have been documented in patients with schizophrenia and their first-degree relatives. More recently, such findings have been extended to first-episode psychotics. At present, it remains under-determined the precise mechanism leading to these impairments, including but not limited to whether any impairments reflect general sensory processing deficits or specific functional deficits in processing particular stimulus properties, as well as whether impairments in one sensory modality are co-occur with those in another sensory modality. We performed electrical neuroimaging analyses of event-related potentials recorded from 16 (all males; 13 right-handed) first-episode psychosis patients and 14 (10 males; 12 right-handed) age-matched controls. The visual task entailed the presentation of Kanizsa-type illusory contour stimuli, allowing for the parallel investigation of impairments in visual sensory processing and completion processes. The auditory task entailed an oddball paradigm. The frequent stimulus (70% of trials) was a 1000Hz centrally-presented sound of 100ms duration. The infrequent stimuli (10% of trials each) varied in pitch (1200Hz), perceived lateralization (700 μ s), or duration (150ms) Remaining parameters matched the frequent stimulus. While we were able to replicate prior findings of impaired early visual responses in first-episode patients using analyses of individual scalp electrodes, this was not evident in analyses of global features of the electric field. By contrast, there was evidence for sensory and functional auditory processing impairments at all levels of analysis. We discuss our findings in the context of attempts to establish biomarkers of psychosis.

I15 Emotion in dreams predicts amygdala response to aversive stimuli

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Background Recent brain imaging studies in humans provide evidence for a role of sleep in emotion brain functions, including the consolidation of emotional memories. Moreover, brain regions involved in the processing of emotions are highly activated during REM sleep, and emotions in dream reports are more intense and negative than emotions experienced during daytime. The observations may reflect emotion regulation processes occurring during sleep. However, the relationship between the processing of emotions during sleep and brain responses to emotions during wakefulness is still highly speculative. Here, we directly addressed this issue by testing whether emotions experienced in dreams correlate with brain responses to emotional stimuli at wake.

Procedure Thirty healthy participants were scanned (3T Siemens Trio) while they watched five photographs of faces with a neutral expression. One of the faces was associated with an aversive white noise. On each morning during the week before the experiment, participants filled a sleep and dream diary, and responded to a series of specific questions about the content of their dreams on that preceding night, particularly about emotions experienced in the dreams. For each participant, the frequency of negative emotions reported in the dreams was computed from these data. The participants also filled a detailed questionnaire about their general dream habits, from which we computed an average frequency of emotion in dreams for each participant.

We analyzed the fMRI data using SPM8. We first compared brain regions more activated for the face paired with the aversive sound (emotional condition) than for other faces (neutral condition). We then performed regression analyses at the group level between these individual contrast images and our measures of dream emotions.

Results The frequency of emotion in dreams did not correlate with measures of anxiety, depression and sleep quality. For the imaging data, as expected, the face paired with the aversive sound activated the pain matrix (insula, medial prefrontal cortex), as well as the auditory cortex and fusiform cortex. Critically, we observed a significant correlation between the response of the amygdala and the fusiform cortex to aversive stimulations and the frequency of negative emotions in both the dream diary and the dream questionnaire.

Conclusion We show that individuals who report more emotional dreams also activate the amygdala more strongly in response to aversive stimuli. This result provides a first support for a link between emotional processes occurring during sleep and emotional brain functions during wakefulness. These findings may also be consistent with the hypothesis that dreams contribute to the regulation of emotion.

I16 Opposing consequences for memory stability when reactivated during waking and sleep

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According to the reconsolidation theory, memories are not consolidated once and forever, but re-enter states of instability whenever they are reactivated during retrieval or by a reminder (Nader & Hardt, 2009). Reactivated memories become again susceptible to disturbing influences and interfering stimuli and need to re-stabilize in order to persist. Reactivations of memories take place at a neuronal level also during sleep, especially slow-wave sleep (SWS). Such reactivations contribute to the facilitating effect of sleep on memory consolidation (Diekelmann & Born, 2010). Odor cues have been found to effectively trigger reactivations of new memories during subsequent SWS (Rasch et al, 2007).

Here, we tested whether memory reactivations during SWS - similar to reactivations during wakefulness - transiently destabilize memory traces. As expected, reactivation during waking destabilized memory traces returning them to a fragile state. However, contrary to our hypothesis, the same odor-cued reactivation stabilized memory traces directly if induced during SWS, even in the absence of subsequent REM sleep. Functional magnetic resonance imaging revealed that reactivation during wakefulness primarily activated lateral prefrontal cortical areas whereas reactivation during SWS mainly activated hippocampal and posterior cortical regions. These results show that reactivation of memory serves distinct but complementary functions depending on the brain state (Diekelmann et al., 2011; Rasch & Born, 2007). We suggest that the evaluative processing of reactivated memories during wakefulness returns these memories to a labile state, allowing for an updating of the memories with new information. Reactivation during SWS, on the other hand, reorganizes and directly stabilizes memories for long-term storage.

J. Disorders of the Nervous System: Basic Mechanisms

J1 Development of high-density scalp somatosensory evoked potential recordings in macaque monkeys

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The goal of the present pilot study was to establish a simple and minimally invasive method to record somatosensory evoked potentials (SSEPs) from the whole scalp surface in anaesthetized adult macaque monkeys using a high-density electrode array. Recordings were performed with a customised EEG cap containing 32 electrodes regularly distributed over the scalp while the monkey was anaesthetized (2.5% sevoflurane). Electrical stimulations were delivered separately either to the median nerve at the wrist or to the tibial nerve at the ankle (0.5Hz repetition rate (1 sweep every 2 seconds), intensity slightly above the visible motor threshold, total of 75 sweeps). The SSEP data were analysed both conventionally in terms of component amplitude and latency at selected scalp locations and topographically by cluster analysis of the voltage maps. This topographical analysis is a data-driven approach and reveals a series of scalp topographies reflecting the steps in information processing. Although responses were somewhat variable in amplitude and latency across the different recording sessions, they were topographically very reproducible. The map topography of the responses obtained after either median or tibial nerve stimulations was in line with the somatotopic organisation of the sensorimotor cortex. Our data show that SSEPs can be successfully and reproducibly recorded from a multichannel EEG cap in macaque monkeys. This minimally invasive method to record large-scale neuronal networks in real-time can be useful if repeated assessment of the cortical activity is desired, for example to study functional damage and recovery after a central nervous system lesion. In this case, topography of SSEPs will allow to assess the possible cortical reorganisation of neuronal networks and relate it to functional recovery. The tool we developed is very relevant in the context of promoting non-invasive approaches also in animal research.

J2 In utero exposure to cocaine impairs postnatal synaptic maturation of glutamatergic transmission in the VTA.

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Maternal exposure to cocaine may perturb fetal development and affect synaptic maturation in the offspring. However, the molecular mechanism underlying such changes remains elusive. We focus on the postnatal maturation of glutamatergic transmission onto mouse ventral tegmental area (VTA) dopamine neurons. We find that during the first postnatal week, transmission is dominated by calcium-permeable (CP)-AMPA and GluN2B-containing NMDA receptors. Subsequently we identify mGluR1 receptors as the key player in the synaptic insertion of calcium-impermeable (CI)-AMPA receptors and GluN2A, a process that does not occur in mGluR1 KO mice. When pregnant mice are exposed to cocaine, this glutamate receptor switch is impaired in offspring by a direct effect of cocaine on the fetal dopamine transporter. Finally, positive modulation of mGluR1 in vivo is sufficient to rescue maturation. Taken together, we identify the molecular target through which cocaine in utero impairs postnatal synaptic maturation, reveal the expression mechanism of this impairment and propose a potential rescue strategy.

J3 Synergistic neurorestorative effects of angioglioneurin Intracerebral administration and environmental enrichment in developing rats

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Molecules with proven neuroprotective, neurogenic, neurotrophic and angiogenic effects, such as VEGF, BDNF, IGF-1 and EPO, decrease in neurodegenerative diseases, stroke, TBIs or ischemia. As they act on all the elements of the neuroglial unit (NVU) as well as the unit as a whole, we propose the term angioglioneurins to define molecules acting on the three components of the NVU. Environmental enrichment (EE) improves brain function in health and disease, including morphological, physiological and behavioural changes at all levels of the NVU. Changes include the increase of neuronal activity and plasticity, glial structure and function and the maturation of the microvascular network. In disease, EE improves functional recovery and prevents neurodegenerative, traumatic, ischemic and even tumoral diseases. These effects are attributed in part to an increase of angioglioneurin production and release. Our aim is to investigate the neurovascular effects of combining VEGF infusion and EE on the visual cortex during the initial days of the critical period. VEGF was administered for one week using intracerebral osmotic minipumps placed in middle cortical layers of P18 Long Evans rats. Different visual stimulation conditions were studied in each experimental group (VEGF infused, PBS infused and non infused controls). Vascular, neuronal and Caspase-3 positive cell densities were measured by the optical disector method. Results showed that the lesion produced by the cannula implantation resulted in decreased vascular, neuronal and Caspase-3 positive cell densities. EE was unable to reverse these effects in any group, whereas VEGF infusion alone partially corrected those effects. A higher effectiveness was reached by combining both the procedures, the most effective combination being when EE was introduced only after minipump implantation. In addition to the angiogenic effect of VEGF, applied strategies also had synergistic neuroprotective effects, and the combination of the two strategies had more remarkable effects than those achieved by each strategy applied individually. EE enhances angioglioneurins expression improving the evolution of most brain diseases. The combination of angioglioneurins administration and EE may be a promising therapeutic strategy for brain restoration.

J4 Activation of innate immunity and alterations glial metabolism in astrocytes in cortical grey matter in multiple sclerosis

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Extended grey matter lesions detected throughout the cerebral cortex shifted substantial attention to grey matter pathology in multiple sclerosis (MS). Emerging as an important correlate of clinical deficits in MS, grey matter abnormalities have been linked to clinical manifestations such as seizures, fatigue and cognitive dysfunction. By investigating otherwise pathological normal grey matter of MS patients, we found a differential expression of genes involved in innate immunity, inflammasome formation and of astrocytic genes known to be involved in energy metabolism and brain homeostasis. Treatment of cortical astrocyte cultures with IL-1b, LPS, ATP or LPS & ATP in vitro led to a similar differential gene regulation highlighting the role of astrocytes in MS. By treatment of mice with the innate immunity stimulating component CFA, reproducing differential gene regulation as seen in MS, we demonstrated that a peripheral innate immune activation greatly affects CNS integrity through astrocytes. These findings highlight a detrimental role of distant chronic inflammation to the structural and functional integrity of cortical grey matter and suggest that these alterations are a major pathogenic component in MS. The astrocytic activation of inflammasomes and the sequential downregulation of metabolic genes important for sustaining neuronal homeostasis might explain fatigue and cognitive dysfunctions encountered in MS patients.

J5 In vitro neurogenic potential of reactive astrocytes isolated from the injured spinal cord

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Reactive astrogliosis is a common phenomenon that occurs after injury or inflammation of the CNS. In the context of spinal cord injury (SCI), quiescent astrocytes surrounding the lesion core acutely respond with increased proliferation and hypertrophy, eventually forming the glial scar. Interestingly, such reactive astrocytes also show expression of early stem cells markers such as Vimentin and Nestin, suggesting a process of cellular de-differentiation. Here we investigate the in vitro proliferative properties of reactive astrocytes using a neurospheres assay. Briefly, GFAP-Cre X Rosa YFP mice were treated for one week with Tamoxifen to induce recombination in GFAP+ astrocytes; one week later mice were subjected to T8 compression SCI. At 4 d.p.i., the lesion tissue was dissociated and single cells were cultured in non-adherent conditions in presence of mitotic factors. An equal-in-weight portion of the intact cervical SC tissue was isolated from the same animals to produce the control culture. While the lesioned tissue displayed high neurosphere-forming potential, the control culture showed an opposite trend. Primary neurospheres were propagated, in subclonal density (10 cells/ μ l), for more than 9 passages. Interestingly, the neurospheres from the "Lesion" culture were enriched in the presence of YFP+ cells compared to control, showing that the progeny of RAs is able to self-renew in vitro. When allowed to differentiate, YFP+ cells from the "Lesion" cultures showed a marked neurogenic potential in early and late passages. Our work suggests that mature astrocytes can undergo a de-differentiation program while reacting to injury, and unambiguously identify Reactive Astrocytes as a source of multipotent, self-renewing stem cells.

J6 Role of FXR in the process of myelination in the peripheral nervous system

Peter Pelsoczi, Olivier Poirot, Roman Chrast

Farnesoid X receptor (FXR) is a transcription factor that plays a fundamental role in regulation of bile acid biosynthesis from cholesterol. FXR regulates expression of genes involved in lipid metabolism and transport, bile acid transport, hepatoprotection and glucose metabolism. Importantly, recently discovered additional functions of FXR in blood vessels, heart, kidney, adrenal gland and adipocytes suggests a more essential function of this receptor than previously anticipated (Asano et al. 2007). We have previously performed microarray analysis of three different models of peripheral neuropathy: PMP22 duplicated, Lpin1 knockout and SCAP knockout mice. We observed that the level of FXR expression was substantially elevated in endoneuria of all three models contrary to its stable level of expression in the dorsal root ganglions (DRGs). This suggested that, in the peripheral neural system (PNS), FXR is mostly expressed in the Schwann cells. We confirmed the glial expression of FXR by quantitative RT-PCR. We have also detected the endoneurial expression of FXR on protein level. An immunofluorescence analysis led to detection of FXR in Schwann cells in sciatic nerve cross sections. These data were further confirmed using cultured Schwann cells, where FXR labeling showed nuclear staining. In order to gain insight into its function in glial cells we performed developmental analysis of FXR expression in developing PNS. We detected a peak of expression around postnatal day 13. This pattern overlapped with the pattern of expression of genes involved in lipid metabolism and in myelin assembly thus strongly suggesting that FXR plays a role in myelination in the PNS. In order to confirm this hypothesis, we are planning to use neuron-Schwann cell co-cultures to study the effects of FXR agonist and antagonist on myelin assembly and maintenance. In addition, we also plan to analyze the PNS phenotype of the recently developed FXR knockout mice.

J7 A new in vitro model to study therapeutic approaches to improve spinal cord regeneration and repair after injury or neurodegenerative diseases

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Both spinal cord injury (SCI) and multiple sclerosis (MS) affect millions of people worldwide with serious clinical consequences. These diseases lead to neuroinflammation and demyelination, both believed to contribute to their phenotypes. Animal models have allowed a number of findings in the fields of repair and regeneration related to SCI and MS. However, such in vivo models are extremely distressful for animals. Moreover, the use of a wide variety of lesion models, and their variability and complexity, limit the ability to identify new therapies. Up to now, no real in vitro alternative exists. We therefore decided to explore organotypic cultures of mouse spinal cord slices ("slice model") that have recently been developed (Bonnici and Kapfhammer, 2008). This "slice model" has already been shown to allow generation of reproducible SCI-like lesions and to study axonal regeneration. We are presently characterizing this "slice model" at the histological and functional levels. We plan to implement and characterize a new demyelination protocol reproducing some pathological changes previously observed in SCI and MS. To confirm the relevance of our model of culture in the SCI and MS field, we will also validate it by testing on it the therapeutic strategies that have been previously successfully used in vivo. By means of these experiments, we hope to demonstrate the possibility to perform SCI and MS-related research without the need of in-vivo models.

J8 Brain Cell Autotransplantation reverses Enkephalin increase in MPTP-treated Monkeys

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Parkinson's disease (PD) is caused by a degeneration of dopaminergic cells in the Substantia Nigra (SN). PD symptoms, like bradykinesia, only appear after a large striatal dopamine depletion. Compensatory mechanisms are probably responsible for this delay in symptoms appearance and may also play a role in new therapies such as stem cell transplantation. In a previous study, we have observed in PD rats that enkephalin (ENK) mRNA striatal expression is modulated even in asymptomatic animals. ENK seems to play a role in the pre-clinical stage of the disease. Our hypothesis was that ENK should be increased in the pre-symptomatic PD phase also in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridin (MPTP) monkeys and that an autologous brain cell transplantation would modulate ENK expression. Eight St. Kitts green monkeys were used for this study and separated into three groups: two normal controls without any intervention, two MPTP controls and four MPTP animals implanted with autologous cultured cells from cortical biopsy. All MPTP monkeys were asymptomatic. Four months after reimplantation, monkeys were sacrificed. TH-immunopositive cells were counted in SN and ENK mRNA expression was measured by in situ hybridization in caudate nucleus and putamen. Preliminary results showed that even in asymptomatic MPTP monkeys, ENK mRNA expression was increased in both caudate nucleus and putamen. Implanted animals presented a decrease of ENK mRNA expression in both caudate and putamen, compared to the normal controls. Our results indicate that there is an ENK increase already in the pre-symptomatic phase. This increase is reversed by an autologous graft, where nigral TH protein expression is back to normal. We suggest that ENK plays a role in the pre-clinical stage of PD. Stem cell transplantation may possibly act by modulating such plastic mechanisms.

J9 Redox dysregulation affects survival, proliferation and differentiation of oligodendrocyte progenitors in model of Schizophrenia

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Schizophrenia is a brain disorder which is caused by the combination of multiple genetic and environmental factors. Converging evidence suggests a role of redox dysregulation in the development of schizophrenia pathophysiology. In particular, genetic and functional data indicate impaired synthesis of glutathione (GSH), the main intracellular antioxidant and redox regulator. Moreover, gene expression profiling, neurocytochemical and neuroimaging studies point to the impairment of oligodendroglia-mediated myelination as a significant feature of schizophrenia. As this process is particularly affected by the redox regulation and oxidative stress, we examined the effect of redox dysregulation induced by a GSH deficit on oligodendrocytes. In vitro, oligodendrocyte progenitors were transduced with lentiviruses encoding siRNA to the catalytic subunit of glutamate-cysteine ligase, the rate-limiting enzyme of GSH synthesis. We found that siRNA were able to significantly decrease GSH levels in oligodendrocyte progenitor cells after seven days of transduction compared with the scramble siRNA. Relatively large GSH deficit (>30%) led to cell death while smaller GSH decrease (~20-30%) induced a reduction in progenitor cell proliferation of 26% without affecting cell survival. Moreover, a GSH deficit (~20-30%) enhances spontaneous differentiation in absence of factors promoting differentiation. These data support a crucial role of GSH in the balance between self-renewing and differentiation of oligodendrocyte progenitors. Thus, the redox dysregulation due to GSH deficit could underly the oligodendroglia-mediated myelination impairment observed in schizophrenia.

J10 Donor Age Affects Creatine-Mediated Induction of Differentiation on Striatal Neural Progenitor Cells

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Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder, characterized by a loss of GABA-ergic neurons in the caudate putamen. Transplantation of neural progenitor cells (NPCs) has emerged as a promising experimental therapeutic strategy for HD, however, the variables responsible for the success of this approach, including the optimal developmental stage of the grafted cells, are largely unknown. The creatine (Cr) kinase phosphotransfer system plays a pivotal role in cells with high and fluctuating energy demands, including neuronal precursors. Supporting cellular energy metabolism by Cr supplementation is a clinically translatable method for improving cell transplantation strategies for HD. We have previously shown that Cr promoted survival and differentiation of cultured rat striatal NPCs. The present study aims at investigating possible differential effects at early (E14) and late (E18) developmental stages. Striatal NPCs were isolated from E14 and E18 rat embryos and cultured for 7 days with and without Cr added at a concentration of 5 mM to the culture medium. Chronic Cr treatment resulted in a significantly increased percentage of GABA-immunoreactive neurons as compared to untreated controls, both in the E14 (170.44 ± 4.67) and E18 group (141.73 ± 8.29). This effect was greater in E14 cultures ($p < 0.01$). Short-term treatment from day in vitro (DIV) 6-7 also resulted in an increased induction ($p < 0.05$) of the GABA-ergic phenotype in E14 (162.97 ± 10.37), as compared to E18 cells (133.27 ± 9.51). Total neuronal cell numbers and general viability, as assessed with the MTT assay, were not affected ($p > 0.05$). Protective effects of Cr against a metabolic insult induced by serum and glucose deprivation were equal in E14 and E18 cultures ($p > 0.05$). In sum, our findings demonstrate that the role of Cr as a GABA-ergic differentiation factor depends on the donor age of striatal NPCs, while Cr-mediated neuroprotection is not significantly influenced by this parameter. These findings may have implications for optimizing cell replacement strategies in HD.

J11 DOUBLE-IMMUNE CHALLENGE WITH THE TOLL-LIKE RECEPTOR 3 AGONIST POLYI:C INDUCES AD-LIKE NEUROPATHOLOGY IN AGED MICE

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Postmortem brain studies consistently reveal strong inflammatory reactions in the vicinity of beta-amyloid (A) plaques and neuronal lesions. However, despite the growing number of studies linking neurotoxic inflammatory responses to Alzheimer's disease (AD) pathogenesis, little information is available on early inflammatory processes which might possess stronger disease-inducing and -modifying potential than A plaque-associated inflammatory responses. We have recently shown that a prenatal immune challenge using the Toll-like receptor-3 agonist and viral mimic PolyI:C (polyriboinosinic acid-polyribocytidilic acid) in wild-type mice causes morphological abnormalities indicative of premature aging. However, neither widespread amyloidosis nor any overt Tau pathology was evident. Here, we tested whether a second immune challenge during adulthood would be sufficient to trigger the development of AD-like neuropathology in aged wild-type mice. We employed two cohorts of mice that were exposed to PolyI:C (5 mg/kg, i.v.) or 0.9% NaCl at gestation day 17. At 8 or 15 months, they were challenged with a second viral-like infection using PolyI:C or NaCl as control. Neuropathological changes, including densities of A and Reelin-positive plaques, phosphorylation levels of Tau, as well as glia activation were analyzed immunohisto- and biochemically 3 months post-treatment. We found a widespread fibrillary amyloid- plaques deposition in the hippocampal formation and neocortex of PolyI:C/PolyI:C-challenged mice compared to controls. Levels of phosphorylated Tau and activated glia cells were also significantly enhanced after a double-immune challenge. These results show that a combined pre- and postnatal viral-like infection can precipitate the development and progression of AD-like neuropathology in aged wild-type animals.

J12 CO-ASSOCIATION OF REELIN AND AMYLOID-BETA IMMUNOREACTIVITY IN RODENT AND HUMAN TISSUE IS ENHANCED IN THE AGED BRAIN

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Age-dependent changes in Reelin-mediated signaling have been suggested to contribute to the neuropathology of late-onset Alzheimer's disease (AD), albeit the molecular mechanisms remain largely unknown. Here, we used biochemical and immunohistochemical techniques to characterize the proteomic composition, localization and temporal progression of Reelin-positive plaques, as well as their potential to sequester A β (Ab) peptides in postmortem human and mouse brain tissue. In samples of non-demented human subjects, Reelin-positive plaques showed the same layer-specific distribution in the hippocampal formation as described in rodents and primates, demonstrating that the occurrence of Reelin-containing plaques is a highly conserved phenomenon of normal aging. Furthermore, applying optimized immunofluorescence protocols, we were able to detect different proteolytic fragments of amyloid precursor protein (APP) in Reelin-positive plaques in both murine and human brain tissues. This co-association was increased in aged brains. Finally, we observed that Reelin immunoreactivity is overall reduced in AD patients as compared to the control group, though only in fornix and entorhinal cortex this difference reached statistical significance. This is in agreement with our previous results demonstrating that the reduction of Reelin expression aggravates AD-like pathology of transgenic mice (tgAPP^{swe,arc:ReIn+/-}). To correlate the neuropathological changes with the Reelin expression in humans, we are investigating putative changes in the methylation status of the Reelin promoter in brains of healthy elderly and AD patients. Taken together, our results support the hypothesis that reduction in Reelin expression below a critical threshold and the perturbation of its signaling accelerates amyloidogenic APP processing and favors both, its own and Ab-aggregation.

J13 Remyelinating lesions express a distinct pattern of genes involved in oligodendrocyte differentiation and proliferation

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Understanding mechanisms of lesion formation, progression and transformation in multiple sclerosis (MS) is essential for improved therapies. Therefore, the identification of factors involved either in one or more of these mechanisms may have therapeutic benefits. By differential gene expression analysis we identified genes being differentially regulated in various MS tissues; normal appearing white matter (NAWM), active lesion, remyelinating lesion and inactive demyelinated lesion. Differential gene expression comparisons between these tissue types identified genes influencing oligodendrogenesis (e.g. FGF2, FGFR1, FGFR4, BMP2 and BMP4) which are highly expressed in shadow plaques but also in active lesions. Cellular localization of a subset of these factors was described by immunohistochemistry, revealing a major expression in astrocytes. By in-situ hybridization, these findings will be further investigated in more detail. The localization of these factors in astrocytes suggests that the decision of repair or gliosis in MS lesions might be highly dependent on astrocytes. These factors involved in oligo- but also astrocytogenesis might drive precursor cells into the astrocyte lineage rather than promoting remyelination. Finally, the simultaneous expression of factors promoting but also inhibiting oligodendrogenesis might leave oligodendrocytes in a pre-mature state, leading to incomplete remyelination and appearance of the so-called shadow plaque.

J14 Anti-hyperalgesic/allodynic properties of the non-benzodiazepine anxiolytic etifoxine in inflammatory and neuropathic pain models

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Persistent pain states resulting from an inflammatory reaction and/or neuropathic insult are associated with the expression of pathological pain symptoms such as mechanical and thermal allodynia. Several studies have shown that the local synthesis of 3 α -reduced neurosteroids (3 α NS), such as allopregnanolone or tetrahydrodeoxycorticosterone, exert an interesting antinociceptive control during pathological pain processing and particularly in the dorsal horn of the rat spinal cord. It is well established that this inhibitory control involves, at least, a direct positive allosteric modulation of GABAA receptor in the spinal nociceptive system. We have moved one step forward in a recent study (Aouad et al, Pain 2009) where etifoxine (EFX), a non-benzodiazepine anxiolytic and a well-described stimulator of neurosteroidogenesis, was shown to strongly reduce and prevent the apparition of generalized neuropathic pain symptoms after treatment with the antitumoral agent vincristine sulfate. We further demonstrated that the observed therapeutical efficacy of EFX in this animal model was carried by the local production of 3 α NS.

In an attempt to extend this interesting finding to other pain states, we have characterized the efficacy of EFX treatment (daily injection at 50mg/kg, i.p.) in rats exhibiting pain symptoms resulting from monoarthritis (complete Freund adjuvant), sciatic nerve compression (cuff) and subchronic treatment with the antitumoral agent oxaliplatin (2 mg/kg, i.p.; 2 injections per week; total of 9 injections). Mechanical and thermal nociceptive thresholds were measured always before the daily injection of EFX using respectively a calibrated forceps and the acetone test. As previously seen in the case of vincristine-induced generalized neuropathy, EFX strongly and rapidly reduced the intensity of mechanical/thermal cold allodynia induced by oxaliplatin chemotherapy within two days of treatment. Appearance of these symptoms was fully prevented if EFX was administered daily but one week before chemotherapy. Interestingly, preventive or curative EFX treatment only reduced the intensity of mechanical hyperalgesia by about 50% in the monoarthritis model. In the sciatic nerve compression model, pain symptoms totally disappeared after a two-week treatment with EFX. They were still absent 4 weeks after the end of the treatment. In conclusion, these experiments show that etifoxine has a powerful and long-lasting analgesic effect in many pathological pain states, at least in animal models. Since this compound is already prescribed as an anxiolytic in several countries around the world and display very limited adverse-effect, it could rapidly be of interest in human pain clinics.

This work is supported by Centre National de la Recherche Scientifique, Université de Strasbourg and by the Institut Universitaire de France.

J15 Effect of anti-Nogo-A antibody treatment in hand dexterity recovery following unilateral hemisection: Electrophysiological study in non-human primates.

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Anti-Nogo-A antibody treatment has shown in both rat and non-human primate to improve recovery of hand dexterity following spinal hemisection. Such behavioral improvement was correlated to new sprouting of corticospinal (CS) axons caudal and rostral to the lesion. Nevertheless, the functional role of such new CS sprouting in the recovery process needed to be assessed. Separately the BDNF has shown to improve axons growth and to be implicating in inhibition of the neurite outgrowth inhibition, so potentially to improve the recovery after a spinal cord injury. In recent work we assessed the effect of combined treatment of anti-Nogo-A antibody and BDNF after a spinal cord lesion in adult macaque monkeys using transcranial electrical stimulation (TES). The obtained results were correlated to behavioral recovery of the hand dexterity. The behavioral and TES data was analyzed in 4 adult monkeys that were submitted to unilateral cervical spinal lesion (C7/C8). Two monkeys were treated intrathecally with anti-Nogo-A antibody and BDNF, whereas a control antibody was infused in the other monkeys. The TES results showed that there were no significant differences between treated and untreated monkeys. These results were correlated with the recovery of the hand dexterity that didn't show any beneficial effects of this combined treatment compared to the control group. Therefore, following these results our ongoing study will investigate the functional role of these new projections only in anti-Nogo-A antibody treated monkeys, using sophisticated methods: stimulus triggered averaging of EMG activity from chronically recorded forelimb muscles in monkeys before and after lesion. In this project, we will focus principally on the primary motor cortex (M1).

J16 Strong Evidence for the Presence of Neuropathy in Myotonic Dystrophy Transgenic Mice Expressing Long CTG Repeats

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Objective: Myotonic dystrophy (DM1, also known as Steinert disease) is characterized primarily by myotonia and muscle weakness and is a multisystemic disorder. Although several studies have been carried out to verify the possible involvement of the peripheral nervous system in DM1, the results have not been univocal and at present, the possible association between peripheral neuropathy and DM1 remains open. Our present study was designed to investigate the presence/absence and the possible type of peripheral neuropathy in a reliable DM1 animal model. Methods: Recently, new transgenic mice (DMSXL) carrying > 1,300 CTGs and displaying severe DM1 features were generated. To investigate whether DMSXL mice show peripheral neuropathy, we measured the evoked compound muscle action potential (CMAP) in gastrocnemius muscles and the nerve conduction velocity (NCV) of the sciatic nerves in control and DMSXL mice. We also estimated the number of motor neurons in lumbar spinal cord segments (L4 and L5) by the physical dissector method. The structure of the sciatic nerve and the neuromuscular junctions (NMJs) on gastrocnemius muscle sections labelled with alphas-bungarotoxin and neurofilament antibody were carefully analyzed. Results: Electrophysiological data recorded from control and DMSXL mice revealed that every DMSXL mouse examined exhibited electrophysiological abnormalities compared to control mice. These abnormalities consisted of a significant decrease in both CMAP parameters and NCV. This result indicates the dysfunction of muscles and peripheral nerves in DMSXL mice compared to control mice. Histological and morphometric analysis showed an axonopathy and neuronopathy in DMSXL mice, characterized by a significant decrease in the number of myelinated motor axons in the sciatic nerve and in motor neurons in lumbar spinal cord region. Also, pathological changes in the size and shape complexity of hind limb end-plates were detected in DMSXL mice. In addition a reduction in the density of acetylcholine receptors on post synaptic membranes was quantitated using the fluorescence intensity. Conclusion: We already shown that transgenic mice expressing the mild DM1 phenotype (carrying 350-500 CTG repeats) do not exhibit any sensory or motor neuropathy (Gantelet et al.2007), therefore the results of our previous and present studies lead us to infer that peripheral neuropathy is linked to a large CTG expansion and a severe form of DM1. (This study is supported by AFM)

K. Clinical Neuroscience

K1 The role of the right parietal cortex in sound localization: a chronometric single-pulse TMS study

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Auditory spatial functions, including the ability to discriminate between the position of nearby sound sources, are subserved by a large temporo-parieto-frontal “where” network. With the aim of determining whether and when the right parietal cortex is critical for auditory spatial discrimination, we applied single pulse transcranial magnetic stimulation (TMS) on right parietal regions 20, 80, 90 and 150ms post-sound 1 onset while participants ($n= 15$ in Exp 1 and $n= 13$ in Exp 2) completed a two-alternative forced choice auditory spatial discrimination task between pairs of sounds presented within the left (Exp 1) or right hemispace (Exp 2). Our results reveal that transient TMS disruption of right parietal activity impairs spatial discrimination when applied at 20 ms post-stimulus onset for sounds presented in the left contralateral hemispace and at 80 ms for sound presented in the right ipsilateral hemispace. We interpret our finding in terms of a critical role for contralateral temporo-parietal networks over initial stages of the building-up of auditory spatial representations and for a right hemispheric specialization in integrating the whole auditory space over subsequent, higher-order processing stages.

K2 Effects of PERIOD3 polymorphism on circadian rhythmicity and sleep homeostasis in healthy older individuals

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Aging is associated with a decrease in non-rapid eye movement (non-REM) sleep consolidation and circadian phase advance, which can reflect changes in the sleep homeostatic and/or circadian drive. In young subjects, a polymorphism of the clock gene PERIOD3 (PER3) can predict inter-individual sleep differences, such as slow EEG oscillations during NREM sleep, REM sleep and wakefulness, with no changes in circadian rhythmicity. Predictors of these inter-individual differences in sleep in older people are still unknown. Here we investigated circadian rhythms and sleep EEG characteristics in older participants homozygous for the longer (PER35/5) and for the shorter (PER34/4) allele of the clock gene PER3. Healthy older volunteers were selected exclusively on the basis of their PER3 genotype, and PER3 polymorphism was determined in 133 participants (55-75 years). Twenty-one PER35/5 and 16 PER34/4 participants completed the 3-week field segment of the study, which comprised actigraphy monitoring and sleep diaries to characterize habitual sleep and wake times. Wake-up times from sleep diaries indicated a tendency for earlier timing for PER35/5 participants. Similarly, actiwatch analysis revealed significant earlier timing of the rest-activity cycle in PER35/5 participants. For the laboratory study, 13 PER35/5 (5 men, 8 women, 62.23 ± 1.01 years) and 13 PER34/4 (5 men, 8 women, 62.38 ± 1.39 years) participants were selected and matched by age, gender, body mass index and ethnicity. Following a baseline night, all volunteers underwent approximately 40 hours of extended wakefulness under constant routine conditions (CR), to assess endogenous circadian phase and amplitude in the absence of the confounding effects of light-dark and behavioural cycles. The CR was followed by a recovery sleep. Circadian rhythms of core body temperature and cortisol did not differ between genotypes. Interestingly, melatonin profile across extended wakefulness revealed that PER35/5 subjects had a phase-advance of fitted melatonin maximum compared to PER34/4 subjects. Sleep structure and consolidation differed between genotypes: Homozygosity for the longer allele (PER35/5) had a significant effect on baseline sleep structure, with lower total sleep time, sleep efficiency, shorter non-REM sleep stage-2 duration, and more wakefulness. Spectral analysis of baseline and recovery sleep EEG activity further indicated differences between the genotypes: EEG delta activity (0.75-1.75Hz) in non-REM sleep was significantly higher (increase of 39.7% for the entire night) and spindle activity (11-13.5Hz) was significantly lower (decrease of 31.9% for all night) in PER35/5 compared to PER34/4 individuals ($p < 0.05$). Within the framework of the circadian and homeostatic regulation of sleep, our data imply for the first time that the interaction of aging and the PER3 VNTR polymorphism affects both the circadian and the homeostatic aspects of sleep regulation. These data have implications for our understanding of the basis of inter-individual differences in age-related changes in circadian rhythmicity and sleep.

K3 Source EEG synchronization topography in Alzheimer's disease

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Introduction Alzheimer's disease (AD) was consistently shown to affect the synchronization of bioelectrical activity between the distributed cortical networks underlying cognition. However, the EEG studies of cooperation between brain networks have been mostly implemented at a sensor level. To overcome possible blurring of the synchronization maps by volume conduction, here we analyzed the topography of synchronization in a 3D source space obtained via an inverse transformation of raw EEG based on biophysically motivated constraints.

Methods Twenty newly diagnosed AD patients (CDR 0.5-1) and 20 controls were recruited from the Memory Clinic of the Neurology Department (CHUV, Lausanne) and local community, respectively. The EEG data were collected while the subjects seated relaxed with closed eyes by a 128-channel Geodesic Sensor Net (EGI Ink., Eugene, OR USA). We digitized (500 samples/s) and filtered (FIR, 1-50 Hz band-pass) raw EEGs. The resulting signals were inverted into scalar sources, modeling local field potentials on the cortical surface by the linear inverse Electra/Laura method (Grave de Peralta Menendez et al. 2004). To this end, we built a forward head model using a high-density MNI cortical mesh of 5124 points and co-registered EGI sensors locations. Subsequently, we computed the corresponding lead-field matrix with a boundary element method. The Laura inverse solution was obtained by mapping individual EEG data on the cortex surface via this lead-field matrix. The resulting signals in the inverse/source space were filtered into four conventional frequency bands, including delta, theta, alpha, and beta. For each band, we computed a Multivariate Phase Synchronization (MPS), which estimates the amount of phase similarity for a population of sources (Strogatz, 2000). Here such a population was defined by a source with all its neighbor sources within the range of 1-3 cm characteristic for superficial association fibers (Carmeli et al., 2005; Fornari et al. 2010). To estimate the whole-brain landscape of synchronization, MPS was computed source-wise. The effects of disease (AD vs. Controls) and of age (<66 years vs. >70 years) were analyzed with a 2-way ANOVA. P-values for all the reported effects were corrected by computing false discovery rates (FDRs < 0.05) with the linear step-up method (Benjamini and Hochberg, 1995).

Results The main effect of AD revealed in patients a specific topography, characterized by a decrease of MPS between the frontocentral sources across all frequency bands and between the left temporal sources in the delta and beta bands. An increase of MPS due to AD was shown in the right parietal (delta band), and bilaterally in the temporal (theta band) cortex. Although the main effect of age factor was not significant, it interacted with AD. This interaction suggested that in the early-onset AD patients MPS changed in the posterior cortical regions of the right hemisphere, whereas in the late-onset AD patients fronto-temporal regions of the left hemisphere suffered first.

Conclusion The whole-brain mapping of multivariate source-EEG synchronization revealed the AD-specific landscape, characterized by anterior hypo-synchronization and posterior hyper-synchronization. The main features of this landscape confirm the results obtained earlier on a smaller sample at an EEG sensor level (Knyazeva et al., 2010). Moreover, the source synchronization provides more precise information as to the topography of early cortical pathology depending on the age of AD onset.

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K4 Circadian sleep-wake cycles and the effect of light treatment in Borderline Personality Disorder

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Objectives: Individuals with Borderline Personality Disorder (BPD) suffer from instable self-image and relationships interacting with emotional instability. Daytime fatigue and sleep disturbances are prevalent. Here, we investigated circadian rhythms, sleep and well-being in women with BPD under their habitual life conditions with light treatment (LT) and without (oLT).
Methods: Fourteen treated and untreated women diagnosed with BPD according to DSM-IV criteria were investigated during 3 weeks without and 3 weeks with morning LT administered at home for 30-40min. Rest-activity cycles were continuously measured using wrist actimetry along with sleep-wake logs, and proximal skin temperature. Saliva samples were collected weekly over a 27-h period to determine the diurnal melatonin rhythm. A range of self-ratings and questionnaires were used to assess depression and clinical state throughout the 6-week protocol. Ten matched healthy women followed the same 6-week protocol without light treatment.
Results: Women with BPD had significantly worse subjective sleep quality, reduced daytime alertness, and higher scores in anxiety, anger and depression than controls. Rest-activity cycles ranged from highly disturbed to extremely regular patterns in women with BPD, thus displaying a significantly higher variance than controls. Morning LT significantly phase advanced activity in BPD compared to oLT, and shortened actimetry-defined sleep episode, which was more relaxed as indicated by decreased nocturnal movement time and increased skin temperature. Daytime alertness improved significantly with morning LT and atypical depression scores were significantly attenuated, whereas general depression scores and borderline symptoms showed no improvement.
Conclusions: Morning LT significantly improved sleep, reduced daytime alertness, and atypical depressive symptoms in women with BPD. Thus, light therapy is a potential adjunct treatment for patients with BPD.

K5 IMPROVING PREDICTION OF PSYCHOSIS BY A MULTI-DOMAIN APPROACH

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Background: Methods for identifying individuals with an At Risk Mental State, ARMS, and predicting their transition to psychosis are still not sufficiently reliable. We therefore investigated if a stepwise enrichment strategy with a multi-domain investigation including neuropsychology, MRI and EEG etc. can improve prediction.

Methods: Within the the Basel FePsy (Früherkennung von Psychosen) study ARMS individuals were identified using first a risk checklist for referrals and then the Basel Screening Instrument for Psychosis BSIP (Riecher-Rössler et al. 2008). From 234 referrals 64 ARMS individuals were identified between March 1, 2000 and February 29, 2004. Fifty-three (83%) could be followed up for up to 7 (mean 5.4) years.

Results: Twenty-one ARSM individuals developed psychosis (transition rate .34). Best transition predictors within this ARMS population were selected attenuated psychotic symptoms (suspiciousness), negative symptoms (anhedonia/asociality), and cognitive deficits (reduced speed of information processing). Overall predictive accuracy was 80.9% (sensitivity 83.3%, specificity of 79.3%) (Riecher-Rössler et al. 2009). Specificity of prediction could be further optimized by EEG and MRI analysis.

Discussion: Identification of ARMS individuals and prediction of transitions could be improved by a stepwise assessment strategy and a multi-domain.

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K6 Hyperprolactinaemia in early psychosis - not only due to antipsychotics

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Introduction: Hyperprolactinaemia is often found in patients with schizophrenia and usually considered a consequence of antipsychotics. It can have many adverse clinical effects. In individuals with an at-risk mental state (ARMS) to our knowledge, prolactin levels have not been investigated up to now.

Methods: Subjects were recruited in the context of the Basel FEPSY Study, a prospective study on the early recognition of psychosis. Prolactin serum levels were measured in 43 ARMS individuals and 26 patients with a first episode of psychosis (FEP). The standardised electrochemiluminescence immunoassay "ECLIA" COBAS®, was used, hyperprolactinaemia was defined as a prolactin level over 95th of the percentile.

Results: Hyperprolactinaemia was found in 25.6% of the ARMS and 46.2% of the FEP.

Within 60 anti-psychotic naïve ARMS and FEP, hyperprolactinaemia was found in 26.7%.

Conclusion: Hyperprolactinaemia in schizophrenia is not necessarily only caused by antipsychotic treatment, but might already be present in neuroleptic naïve FEP and even in prodromal stages. As prolactin is a "stress hormone", these findings shed an interesting light on potential pathogenetic mechanisms of psychosis. Clinically our findings support that prolactin should be measured before introducing antipsychotics in FEP patients. If serum prolactin levels are already increased, clinicians should consider choosing prolactin sparing neuroleptics.

K7 Pituitary volume increase during emerging psychosis

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Background: Morphologic abnormalities of the pituitary gland volume (PV) have been reported in schizophrenia, but at what point in time they occur remains unclear. This study determines PV across different stages of emerging psychotic disorders compared to healthy controls. **Methods:** We compared PV of 36 individuals with an at-risk mental state (ARMS) for psychosis, 23 patients with a first episode psychosis (FEP) and 20 healthy controls (HC). Transition to psychosis was monitored using the BPRS transition criteria according to Yung et al. Applying these transition criteria, 16 of the 36 ARMS individuals made the transition to psychosis (ARMS-T) and 20 did not (ARMS-NT). We traced PV manually on 1 mm slices of magnetic resonance images in three dimensions (coronal, sagittal and axial) blind to group status. We used univariate analysis of covariance (ANCOVA) with PV as dependent variable, group and sex as between-subject factors and whole brain volume as covariate. **Results:** PV increased from HC to ARMS-NT to ARMS-T/FEP. ANCOVA revealed a significant effect of group ($F_{3,78} = 3.0$; $p = .036$) and a sex x group interaction ($F_{3,78} = 6.5$; $p = .001$). Over all groups, women had considerably larger PV than men ($F_{1,78} = 9.8$; $p = .003$). **Conclusions:** Our findings provide further evidence that PV is increased with emerging psychotic disorders, and suggest that this is due to a stress-associated activation of the pituitary gland.

K8 Increased serum BDNF levels correlate with therapy response and improvement in psychological functioning in patients with major depressive episode

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Purpose of the study: Depression is one of the most prevalent forms of mood disorders. Compelling evidence suggests that mood disorders are characterized by reduced neuronal plasticity, which can be brought about by exposure to stress. Furthermore, there is good agreement in considering key proteins such as the brain-derived neurotrophic factor (BDNF), as a central player for the effects of stress on brain function and plasticity and psychopathological implications. Still, there is a high non-responder rate in antidepressant therapy, which explains the need to find reliable predictors for adequate treatment. Previous studies revealed that plasma and serum BDNF levels in depressed patients were significantly lower than in healthy controls. Since the protein can cross the blood brain-barrier serum content correspondingly correlates with cortical BDNF concentrations suggesting BDNF levels as a promising candidate biomarker for depression and antidepressant treatment response. **Methods:** To investigate the association between BDNF serum levels and treatment outcome, blood was drawn from 28 patients with a major depressive episode (DMS-IV, ICD-10) that participated in a double-blind placebo controlled treatment study [1]. All patients were treated with a stable mirtazapine monotherapy. Partial sleep deprivation (PSD) was performed after one week. Placebo controlled additional morning treatment with the stimulant modafinil was started during PSD and maintained over two weeks. Serum concentrations of BDNF were assessed by an enzyme-linked immuno absorbent assay (ELISA) from day 1 ("before PSD") and day 2 ("after PSD"). Samples were diluted 1:100 and detection of soluble BDNF was carried out in an antibody sandwich format. All assays were carried out in duplicates and means were calculated for the corresponding group. Moreover, sleep EEG and microsleep episodes were recorded with a portable EEG. Depression severity using the Hamilton Depression Rating Scale and mood, tiredness and relaxation were assessed with visual analog scales (VASs) for psychological functioning at days 1, 2 and 3 ("after recovery night") as well as after one and two weeks of ongoing treatment. **Results:** After PSD, serum of depressive patients exhibited a significantly ($p < 0.01$) increased BDNF content ($15.57 \pm 1.2 \text{ ng/ml}$) when there was an additional treatment during PSD with the stimulant modafinil compared to the stably treated mirtazapine group ($11.65 \pm 0.76 \text{ ng/ml}$) without additional stimulant. Enhanced BDNF serum levels after PSD were prominent in all patients identified as responders after 2 weeks of follow up. In addition we were able to show that high BDNF serum levels after PSD reflected mood improvement, and increased relaxation. Furthermore it seems that PSD exhibits an acute effect on the endocrine stress response. This could be shown by significantly increased morning serum cortisol levels after PSD in the stably mirtazapine treated group ($219.7 \pm 18.35 \text{ ng/ml}$) compared to baseline ($171.2 \pm 9.56 \text{ ng/ml}$). Of note, patients additionally treated with the stimulant modafinil did not show an acute endocrine stress response after PSD indicated by unchanged cortisol levels compared to baseline suggesting an attenuating effect of the drug on the stress hormone axis regulation. **Conclusion:** Altogether, we conclude that an increase in BDNF is linked to a positive treatment response and improvement in psychological functioning which indicates that serum BDNF levels could be used as reliable predictor for therapy outcome.

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K9 Reading without seeing: Early effects of emotional words on event-related potentials in cortical blindness

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Previous evidence in brain-damaged patients indicates that some stimuli can be detected in the absence of visual cortex (blindsight), presumably involving an alternative “fast” visual route via the superior colliculi and the pulvinar. Although blindsight is usually observed for relatively simple visual attributes (shape, location), some findings suggest that emotional information conveyed by complex stimuli such as faces might also be extracted without visual awareness in cortically blind patients (affective blindsight). However, it is unknown whether these effects may extend to emotional words. Further, the underlying neural processes are still debated. Here we measured EEG during visual presentation of thirty emotionally positive, negative, and neutral words to a 65-year-old cortically blind male patient (SR) with bilateral occipital stroke and anosognosia (Anton Syndrome). After the task, the patient was unable to remember any of the presented words. Nevertheless, event-related potentials showed an early processing advantage for emotional words, with significantly increased N1 amplitude, but also a main effect of repeated word presentation, possibly reflecting repetition suppression. These preliminary findings suggest that the primary visual cortex might not be necessary to unconsciously detect the meaning, and modulate processing of emotional words in intact extrastriate visual areas.

K10 Different duration of at-risk mental state associated with neurofunctional abnormalities – A multimodal imaging study

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Objectives: Neurofunctional alterations are correlates of vulnerability to psychosis, as well as of the disorder itself. However, neurofunctional abnormalities within the ARMS, and how they relate to different probabilities for later transition to psychosis is unclear. We investigated neurofunctional abnormalities during working memory processing in individuals with an at-risk mental state (ARMS).

Experimental design: Patients with ‘first-episode psychosis’ (FEP, n=21), short-term ARMS (ARMS-ST, n=17), long-term ARMS (ARMS-LT, n=16), and healthy controls (HC, n=20) were investigated with an n-back working memory task. We examined functional (fMRI) and structural magnetic resonance imaging (sMRI) data in conjunction using Biological Parametric Mapping (BPM) toolbox.

Principal observations: There were no differences in accuracy, but the FEP and the ARMS-ST group had longer reaction times compared to the HC and the ARMS-LT group. With the 2-back>0-back contrast we found reduced functional activation in ARMS-ST and FEP compared to the HC group in parietal and middle frontal regions. Relative to ARMS-LT individuals, FEP patients showed decreased activation in the bilateral inferior frontal gyrus and insula, and in the left prefrontal cortex. Compared to the ARMS-LT, the ARMS-ST subjects showed reduced activation in the right inferior frontal gyrus and insula. Reduced insular and prefrontal activation was associated with gray matter volume reduction in the same area in the ARMS-LT group.

Conclusions: These findings suggest that vulnerability to psychosis was associated with neurofunctional alterations in frontotemporo-parietal networks in a working memory task. Neurofunctional differences within the ARMS were related to different duration of the prodromal state and resilience factors.

K11 Verbal episodic memory deficits in patients with first episode psychosis and individuals with an at risk mental state

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The present study compares different aspects of verbal episodic memory (VEM) in at risk mental state for psychosis individuals (ARMS) and patients with a first episode of psychosis (FE). 14 ARMS individuals who transitioned to psychosis (ARMS-T) in follow-up, 24 ARMS without later transition to psychosis (ARMS-NT), 38 FE and 41 healthy control subjects (HC) were assessed with the California Verbal Learning Test (CVLT). Our hypothesis was that FE are most severely impaired while, ARMS-T show similar but less severe deficits. ARMS-NT were expected to show minor deficits compared to healthy controls (HC). Thus, we expected the following sequence in performance in VEM: HC>ARMS-NT>ARMS-T>FE. This sequence in performance was statistically tested using the Jonkheere Terpstra Test. Post-hoc Bonferroni corrected Mann-Whitney-U tests compared patients to HC. Potential confounders such as age, gender, education, medication, use of cannabis were controlled. The sequence in performance (HC>ARMS-NT>ARMS-T>FE) was confirmed for CVLT variables that can be explained by encoding deficits ($p .02$), but not for variables explainable by deficits in retention. Compared to HC, FE were significantly impaired in most "encoding" variables ($p .02$), while ARMS-T showed less severe impairments and were only significantly impaired in Sum of Trials 1-5 ($p .04$). As expected, ARMS-NT showed no significant impairment at all. Conclusively, measurement of encoding might be helpful in the differential diagnosis of ARMS-T versus ARMS-NT.

K12 Comparison of clinical routine EEG and quantitative EEG in first episode of psychosis and At-Risk Mental State individuals

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Introduction: Intermittent focal or general pathological slow wave activity detected in routine clinical EEG assessment is more prevalent in patients with a first episode of psychosis (FE) and At-Risk Mental State (ARMS) than in normal controls and helps, in conjunction with psychopathological symptoms, to correctly predict a first psychotic episode in ARMS individuals. We hypothesize that ARMS individuals and FE showing intermittent focal or general slow wave pathology are characterized by an elevated global field power density in the delta and theta range, and that this finding predicts psychosis in ARMS individuals in a similar way as does routine clinical EEG assessment.

Methods: EEG of 27 FE and 32 ARMS subjects were recorded under resting state conditions with eyes closed. Two blinded neurologists analyzed the EEGs visually for presence of focal or general slowing and epileptiform discharges. Additionally, Fast Fourier Transform was performed utilizing Brain Vision Analyzer®. The power spectrum was subdivided into 7 bands and was plotted according to the presence and absence of intermittent slow wave activity. An optimal range was defined in order to quantify what in clinical EEG assessment is coined as pathological slow wave activity. Logistic regression analysis was performed to predict incidence of psychosis.

Result: Individuals with intermittent slow wave pathology were characterized by a range of increased theta activity (4 - 7Hz) ($t=-2.9$; $df=20.1$; $p=.008$). This range has been derived as optimal in terms of a maximal power difference between those with and without intermittent slow wave pathology and a minimal number of bins used. However, there was no power difference in this range with regard to a later onset of psychosis nor was any predictive power related to it.

Conclusion: focal or general slow wave pathology in ARMS individuals and FE is reflected by a range of increased power density related to the theta band, but the increase detected in global field analysis is modest due to its restricted manifestation in time and/or space. Therefore, automated global field power analysis cannot replace clinical EEG assessment for the prediction of psychosis.

K13 Virtual reality for motor rehabilitation and functional pain treatment in incomplete SCI patients

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Spinal cord injury (SCI) causes both long-lasting lower limb motor dysfunction and associated neuropathic pain. Currently, although these two conditions share related cortical mechanisms, pharmacological interventions are used for neuropathic pain and physiotherapy for motor dysfunction. Interventions which directly address both neuropathic pain and motor dysfunction may thus bring substantial benefits to incomplete SCI (iSCI) patients. We are creating the first virtual reality (VR) training system combining action observation and execution to treat motor dysfunction and neuropathic pain using motivating games. It is known that execution and observation of goal-directed actions activates overlapping cortical networks ("mirror system") (Rizzolatti and Craighero 2004), even in chronic SCI patients. There is also evidence that neuropathic pain in iSCI patients can be reduced using motor imagery and visual illusions of virtual limbs (Moseley 2007). Therefore, with intensive training using entertaining games on our VR system, we may be able to reshape cortical networks to simultaneously improve motor function and reduce neuropathic pain in iSCI patients. Our project combines technology development, clinical testing and neuroimaging studies. To interface to the VR system we are developing size-adjustable wearable shoe sensors to measure both foot pressure distribution and leg/foot angles. The clinical studies will test the hypotheses, in chronic and acute iSCI patients, that training with our VR system reduces neuropathic pain and improves lower limb function. The neuroimaging studies examine the relationships between real and attempted action observation, imitation and goal-directed execution in healthy volunteers and iSCI patients. We expect to see training-related changes in cortical activity corresponding to reductions in neuropathic pain and improvements in motor function in patients. So far, in this project we have produced a first prototype of the VR system and completed a first fMRI study in healthy subjects. The neuroimaging study is the first to show fMRI activation resulting from combined observation and imagination of lower limb movements. In future activities we will test spinal cord injury patients in the same paradigm to track the effect of VR training on brain activity. We have also started usability and clinical testing of the VR system in iSCI patients, and will further refine the design of the VR system.

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Supported by the International Foundation for Research in Paraplegia (IRP) and the Swiss National Science Foundation (SNF), grant number PMPDP3-124282/1.

K14 POTASSIUM CHANNEL ALTERATIONS MEDIATE PERIPHERAL NERVE HYPEREXCITABILITY IN A MOUSE MODEL OF TYPE 2 DIABETES MELLITUS

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Diabetes mellitus (DM) is a major cause of peripheral neuropathy. More than 220 million people worldwide suffer from type 2 DM, which will, in approximately half of them, lead to the development of diabetic peripheral neuropathy. While of significant medical importance, the pathophysiological changes present in DPN are still poorly understood. To get more insight into DPN associated with type 2 DM, we decided to use the rodent model of this form of diabetes, the db/db mice. During the in-vivo conduction velocity studies on these animals we observed the presence of multiple spiking followed by a single stimulation. This prompted us to evaluate the excitability properties of db/db peripheral nerves. Ex-vivo electrophysiological evaluation revealed a significant increase in the excitability of db/db sciatic nerves. While the shape and kinetics of the compound action potential of db/db nerves were the same as for control nerves, we observed an increase in the after-hyperpolarization phase (AHP) under diabetic conditions. Using pharmacological inhibitors we demonstrated that both the peripheral nerve hyperexcitability (PNH) and the increased AHP were mostly mediated by the decreased activity of Kv1 channels. Importantly, we corroborated these data at the molecular level. We observed a strong reduction of Kv1.2 channel presence in the juxtaparanodal regions of teased fibers in db/db mice as compared to control mice. Quantification of the amount of both Kv1.2 isoforms in DRG neurons and in the endoneurial compartment of peripheral nerve by Western blotting revealed that less mature Kv1.2 was integrated into the axonal membranes at the juxtaparanodes. Our observation that peripheral nerve hyperexcitability present in db/db mice is at least in part a consequence of changes in potassium channel distribution suggests that the same mechanism also mediates PNH in diabetic patients.

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