# Full Abstracts

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## A. Development of the Nervous System

### A1 Calsyntenin-Mediated Trafficking of Axon Guidance Receptors Regulates the Switch in Axonal Responsiveness at Choice Points

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During the development of the nervous system, growing axons must find their correct targets in order to form a functional neural network. In order to understand the molecular background of axon guidance, we must understand how growing nerve fibers are led to their target cells. The dorsal commissural neurons are a well-established model system to investigate the molecular mechanisms of axon guidance, as their axons always grow in a stereotypic and characteristic manner. Axons extend from the dorsal location of the cell bodies to the ventral midline, where they cross the floor plate and then, after a sharp turn, grow in rostral direction along the contralateral floor-plate border. Along their trajectory growing axons navigate with the help of guidance cues, which either attract or repel them. In order to respond to these cues, the axonal growth cones must carry distinct receptors on their surface. We show that intracellular trafficking is a crucial regulatory mechanism for axon guidance by delivering specific receptors to the growth cone surface. Calsyntenin1, a transmembrane protein expressed in growth cones, links vesicles containing distinct cargo to kinesin motors and is thus involved in fast anterograde axonal transport. We identified Calsyntenin1 as a co-regulator of floor-plate exit and the contralateral turning decision of dorsal commissural axons by regulating surface levels of two specific guidance cues, Robo1 and Frizzled3.

### A2 Role of Wnt Signalling in Commissural Axon Guidance

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For the formation of neural circuits, axons have to be guided to their appropriate target cells by a combination of attractive and repulsive cues. Recently, we have shown that Wnt5a and Wnt7a act as attractants for post-crossing commissural axons in the spinal cord of chicken embryos. However, the molecular signaling pathways activated by Wnts during axon guidance are not completely understood. In addition to atypical protein kinase C, members of the Wnt planar cell polarity (PCP) pathway were implicated in commissural axon guidance in the mouse. We confirmed that PCP components are also required for post-crossing commissural axon guidance in the chicken spinal cord. However, we found evidence for a contribution of the canonical Wnt pathway to post-crossing commissural axon guidance. Taken together, these studies show that Wnt signaling in axon guidance cannot be reduced to one of the well-known signaling pathways. Rather, Wnt activates a complex network of intracellular signaling components.

## A3 Role of DiGeorge Critical Region 2 gene in cortical circuit formation

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Alterations in the generation, migration and integration of different subtypes of neurons in cortical circuits could play a critical role in the vulnerability to schizophrenia. Using in vivo cell-type specific manipulation of pyramidal neurons progenitors, we aim to investigate the role of DiGeorge Critical Region 2 (DGCR2) on cortical circuit formation. DGCR2 is a schizophrenia-risk gene that is affected in the 22q11 microdeletion syndrome, one of the highest known risk factors for schizophrenia. Interestingly whole exome sequencing revealed a de novo DGCR2 mutation in an idiopathic schizophrenic patient (Xu et al., 2011, Nature Genetics), further supporting the importance of this gene in schizophrenia risk. DGCR2 codes for an adhesion protein expressed during cortical development indicating that it could regulate cellular processes such as neuronal migration. Here we show that shRNA mediated down-regulation of the expression of DGCR2 during corticogenesis, by in utero electroporation, dramatically affects the migration of neuronal progenitors at postnatal day 0 and 7 in 2 different brain regions: the somatosensory cortex and the medial prefrontal cortex. This alteration of migration is fully rescued by co-electroporating an shRNA resistant construct of DGCR2 with the shRNA. In order to better understand the biological function of this gene, we will investigate the role of specific domains of DGCR2 using truncated constructs and targeted mutations. Finally we aim to study the functional and behavioural consequences of prefrontal cortex shRNA-DGCR2 alterations induced during development. Taken together these studies will allow us to understand the role of DGCR2 in cortical circuit assembly and study the impact of specific prefrontal cortex microcircuit developmental alterations on the emergence of schizophrenia-related phenotypes.

## A4 Effects of altered expression of SynCAM1 and Neuroligin-1B on adult-born neuron integration and survival

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Hippocampal adult neurogenesis results in the formation of new neurons in the adult hippocampus and participate to learning. The maturation and survival of new neurons is regulated by their activity during the first month after division. Here, we tested whether enhancing excitatory synaptogenesis may increase new neurons' survival and maturation during this critical developmental phase. We tested the effect on the integration and survival of two cell adhesion molecules, SynCAM1 and Neuroligin-1B (NL1B), which are known to increase excitatory synaptic efficiency and dendritic spine formation, respectively. We used a viral-mediated cell specific gene delivery approach to selectively overexpress SynCAM1, SynCAM1 dominant negative isoform or NL1B in adult-born hippocampal neurons in wild-type mice. We then assessed changes in neuronal survival and maturation using confocal microscopy. We found that SynCAM1 and NL1 induced distinct enhancements of dendritic maturation, spine density and morphology, pointing to complementary effects on the excitatory input of newborn neurons.
These results indicate that the cell-autonomous overexpression of synaptic adhesion molecules induce the maturation of newborn neurons and their integration into the hippocampal network.

## A5 Effects of antagonizing Nogo-1 receptor on survival and morphological differentiation of dopaminergic neurons in mesencephalic cultures

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The myelin associated protein Nogo-A in combination with its receptor NgR1 is a potent growth inhibitor of the adult CNS. Nogo-A is mostly expressed on the surface of oligodendrocytes, but recently also reported to be present in neurons including dopaminergic neurons. These findings suggest that Nogo-A serves additional functions in the brain. So Nogo-A has been recently shown to restrict synaptic plasticity in the hippocampus and that its inhibition enhances growth and reactive sprouting in organotypic hippocampal slice cultures. In the present study, we investigated the effects of antagonizing NgR1 on cultured dopaminergic neurons. For that purpose ventral mesencephalic cultures from E14 rat embryos were grown in absence or presence of the NgR1 antagonist NEP1-40 for one week. Treatment with NEP1-40 resulted in significantly increased cell densities of tyrosine hydroxylase immunoreactive neurons. Morphological analyzes of tyrosine hydroxylase -positive neurons revealed longer neurites and higher numbers of primary neurites in cultures incubated with NEP1-40, while soma size was not changed. Moreover, organotypic ventral mesencephalic cultures displayed significantly bigger volume and higher tyrosine hydroxylase positive cell numbers after NEP1-40 treatment. In sum, our findings demonstrate that the intervention of Nogo-A signaling by antagonizing NgR1 modulates dopaminergic neuron properties in the developing midbrain. Furthermore, these observations hint to the idea that Nogo-A signaling might play a role in the pathophysiology of Parkinson's disease.
Supported by SNF and the Swiss Parkinson Foundation.

## A6 Retinal Input Directs the Recruitment of Inhibitory Interneurons Into Thalamic Visual Circuits

**Authors**

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Inhibitory interneurons (IN) critically control the excitability and plasticity of neuronal networks, but whether activity can direct IN into specific circuits during development is unknown. Here, we report that in the dorsal lateral geniculate nucleus (dLGN), which relays retinal input to the cortex, circuit activity is required for the migration, molecular differentiation, and functional integration of IN. We first characterize the prenatal origin and molecular identity of dLGN IN, revealing their recruitment from an Otx2+ neuronal pool located in the adjacent ventral LGN. Using time-lapse and electrophysiological recordings, together with genetic and pharmacological perturbation of retinal waves, we show that retinal activity directs the navigation and circuit incorporation of dLGN IN during the first postnatal week, thereby regulating the inhibition of thalamocortical circuits. These findings identify an input-dependent mechanism regulating IN migration and circuit inhibition, which may account for the progressive recruitment of IN into expanding excitatory circuits during evolution.

### A7 Delay of cortical thinning in very preterm born children

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Background: Cortical gray matter thinning occurs during childhood due to pruning of inefficient synaptic connections and an increase in myelination. Preterms show alterations in brain structure, with prolonged maturation of the frontal lobes, smaller cortical volumes and reduced white matter volume. These findings give rise to the question if there is a differential influence of age on cortical thinning in preterms compared to controls.

Aims: To investigate the relationship between age and cortical thickness in preterms when compared to controls.

Methods: Forty-one preterms (< 32 weeks gestational age and/or < 1500 gram birth weight) and 30 controls were included in the study (7-12 years). The automated surface reconstruction software FreeSurfer was applied to obtain measurements of cortical thickness based on T1-weighted MRI images.

Results: Cortical thickness was lower in bilateral frontal and left parietal regions and higher in left temporal gyri in preterms compared to controls. However, these differences depended on age. In preterms, age correlated negatively with cortical thickness in right frontal, parietal and inferior temporal regions. Accordingly, cortical thickness was higher in young compared to old preterms in bilateral frontal, parietal and temporal regions. In controls, age was not associated with cortical thickness. Conclusion: In preterms, cortical thinning still seems to occur between the age of 7 and 12 years, mainly in frontal and parietal areas whereas in controls, a substantial part of cortical thinning appears to be completed before they reach the age of 7 years.

These data indicate slower cortical thinning in preterms than in controls.

## B. Molecular and Cellular Mechanisms: Cell-Cell Interaction

### B1 Intracellular potassium concentration in astrocytes is under the influence of both extracellular potassium levels and glutamate transport

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Astrocytes have a central role in regulating K+ and glutamate, both released by neurons in the extracellular space during synaptic activity. Glial glutamate uptake is a secondary active process that involves the influx of three Na+ ions and one proton and the efflux of one K+ ion. Thus, intracellular K+ ([K+]i) is potentially influenced both by extracellular K+ concentration ([K+]o) fluctuations and glutamate transport activity in astrocytes. We evaluated the impact of these K+ ion movements on [K+]i in primary mouse astrocytes, monitored by microspectrofluorimetry using the recently developed K+ sensitive fluorescent probe Asante Potassium Green-1 (APG-1). An in situ calibration procedure enabled us to estimate the resting [K+]i at 133±1mM. We first investigated the dependency of [K+]i levels on [K+]o and switched [K+]o from 3, to 5.4, 10 and 15mM. We found that [K+]i was adjusting to [K+]o changes nearly proportionally (slope=0.73±0.04), which is compatible with the reported high K+ conductance of astrocyte membranes. We then found that glutamate superfusion (200µM) caused a reversible drop of [K+]i that depended on the glutamate concentration with an apparent EC50 of 10.5±0.9µM, corresponding to the affinity of astrocyte glutamate transporters. The amplitude of [K+]i drop was found to be 2.3±0.1mM

for 200µM glutamate applications. Interestingly, glutamate application synchronized with a [K+]o switch from 5.4 to 3mM led to a further modulation of the [K+]i response than that observed in a steady-state 3mM [K+]o situation, a phenomenon recently attributed to a [K+]o-control of glutamate transporter kinetics. Overall, we showed for the first time that [K+]i undergoes significant decrease in response to glutamate application as well as a modulation of this response by [K+]o itself. This regulation raises important questions regarding interactions between K+ and glutamate homeostasis as well their impact on network properties and energy metabolism.

## B2 Umbilical Cord Mesenchymal Stem Cells Secretome Induces Gliogenesis

**Authors**

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Objective: Mesenchymal stem cells (MSC) have been proposed as a promising tool for the treatment of perinatal brain damage and other central nervous system disorders. Their secretome has been shown in vitro and in vivo to have beneficial effects on neurogenesis and neuroregeneration. Wharton's Jelly (WJ) seems to be an ideal source of MSC. Therefore, the objective is to assess the effect of the neurotrophic factors from WJ-MSC on neuroregeneration in vitro.
Methods: The expression of neuroglial markers of rat neural progenitor cells (NPC) after treatment with MSC-conditioned medium (CM) or direct co-culture was assessed by immunocytochemistry, real-time PCR and flow cytometry. Time points of measurement were after 48 and 96h. Furthermore, the differences between WJ-MSC harvested from term or pre-term pregnancies were evaluated.
Results: Hippocampal NPC at passage 3 after being exposed to CM or in direct contact to MSC showed an increased expression of glial markers such as glial fibrillary acidic protein (GFAP) or myelin basic protein (MBP). Time points of measurement didn't have a significant influence. Interestingly, MSC from term pregnancies were able to induce more strongly the expression of glial markers when compared to preterm. The co-culture compared to the CM had a more prominent effect on the expression of glial markers.
Conclusions: Soluble factors of MSC from term or preterm pregnancies increase the expression of neuroglial markers GFAP and MBP in NPC. These findings indicate a possible supportive role of transplanted WJ-MSC in the neuro-regenerative potential of endogenous NSC.
Financial support by Cryosave Switzerland and The Eagle Foundation.

## B3 The ultrastructure of adult neural stem cells in the hippocampal neurogenic niche

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Deep in the dentate gyrus lie the radial glia-like (RGL) stem cells; the cornerstone of a production line that supplies the hippocampus with new neurons throughout adult life. The bodies of these self-renewing stem cells sit in the subgranular zone of the dentate gyrus, but their processes stretch across the granule cell layer, squeezing through the tight gaps between mature granule cells. Once clear of the granule cell layer these processes split into finer and finer threads, forming dense webs across the molecular layer. Upon activation, RGL stem cells can divide and differentiate into new neurons, but before they do, they retract their complex processes, begging the question: what purpose do these processes serve?
We sought to answer this question by first examining the ultrastructure of RGL stem cell processes using light and electron microscopy. RGL stem cells, identified by their expression of Nestin and their distinctive morphology, were examined in Nestin- GFP transgenic mice.

Their processes were then labelled using either an immunogold or an immunoperoxidase protocol. Subsequent light and electron microscopic analyses revealed that the fine processes took the form of long beaded strings, displaying regular varicosities. Branching from these varicosities were yet finer processes that wrapped around synapses in their immediate vicinity, in a similar fashion to the processes of astrocytes. Processes also appeared to wrap around nearby blood capillaries, with a pronounced thickening and higher numbers of cytosolic mitochondria at the points of their intersection.

These findings introduce the possibility that stem cell function might be controlled by an interaction between neuronal or vascular networks and the processes of the stem cell. The next step will be to investigate the exact nature of this interaction, to ascertain the specific factors that influence the lives of adult neural stem cells.

## B4 Implication of astrocytes in a mouse model of spontaneous oscillatory neuronal activity

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Astrocyte implication in neuronal activity has mostly been evidenced using electrical or pharmacological stimulation to evoke neuronal activity. Whether similar interactions are found in the context of physiological neuronal activity needs to be considered. We implemented an acute slice mouse model displaying spontaneous oscillatory activity of layer 3 entorhinal neurons to study electrophysiological changes in astrocytes arising from this neuronal activity. We simultaneously recorded the membrane potential of individual astrocytes and neuronal network activity using whole-cell patch-clamp and field potential, respectively, with electrodes placed 50-100m apart. Oscillatory neuronal activity consisted in Up-states lasting ~5s alternating with Down- states at <0.1Hz. Astrocytes displayed depolarizations of ~2mV during Up-states that were neuronal-activity dependent as they matched neuronal Up-states in frequency, duration, and amplitude. Both activities were modulated in frequency and amplitude by carbachol and abolished by CNQX or TTX application. The nature of ion movements involved in astrocytic depolarization was then investigated. The contribution of electrogenic glial glutamate uptake (together with the entry of 3Na+, 1H+ and exit of 1K+) was prevented by applying the specific inhibitor TFB-TBOA (100nM). Under glutamate transporter inhibition, neuronal Up-states increased in frequency; however synchronized astrocytic depolarizations were maintained. K+ uptake was then blocked using the astrocytic K+ inward rectifying channel blocker Ba2+ (25-100µM). Under these conditions, both neuronal and astrocyte oscillatory activities disappeared. These experiments underline the ability of astrocytes to keep neuronal activity under control by monitoring and regulating the extracellular space homeostasis. The spatial and temporal aspects of these events as well as the extent of glial syncytium participation will be further investigated.

## B5 De-novo expression of parvalbumin in ependymal cells in response to brain injury promotes ependymal niche remodeling

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The calcium-binding protein parvalbumin (PV) hallmarks subpopulations of interneurons in the murine brain. We serendipitously observed the de-novo expression of PV in ependymal cells of the lateral ventricle wall following in-vivo lesioning and the preparation of organotypic hippocampal slice cultures (OHSCs). In OHSCs, de-novo PV-expression begins shortly after the onset of culturing, and the number of ependymal cells implicated in this process increases with time. PV-immunopositive ependymal cells aggregate and form compact cell clusters characterized by lumen-formation and beating cilia. Numerous single cells acquire a reactive phenotype and undergo marked alterations in shape. Exposure of OHSCs to NF-B inhibitors and to antioxidants reduces PV-expression in ependymal cells, thereby implicating this process in injury-induced inflammation. Indeed, in-vivo stab injury enhances PV-expression in ependymal cells adjacent to

the lesion. Such reactions are not observed in PV- knock-out mice, which manifest an impaired wound-healing response to in-vivo injury, and profound cell-morphological alterations in OHSCs. Whole-transcriptome analysis of ependymal-cell clusters in OHSCs revealed down-regulation of genes involved in cytoskeletal rearrangement, cell motility and cell adhesion in PV-KO as compared to wild-type mice, whereas those implicated in the response to hypoxia and oxidative stress were up-regulated. Our data indicate that the injury-triggered up-regulation of PV-expression is mediated by inflammatory cytokines, and promotes the motility and adhesion of ependymal cells, thereby contributing to the reestablishment of a continuous ependymal cover.

## C. Molecular and Cellular Mechanisms: Signaling

### C1 Structural analysis of synaptic vesicle exocytosis by correlative cryo-fluorescence microscopy and cryo-electron tomography in rat synaptosomes

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As the central event of information processing, learning and memory as well as for the coordination of body functions, it is important to understand synaptic vesicle exocytosis in both health and disease. At the chemical synapse signal transduction is mediated by releasing neurotransmitter molecules into the synaptic cleft. The neurotransmitter is packaged into synaptic vesicles and stored at distinct pools of vesicles within the synapse. The pool of ready to release vesicles is tethered to the active zone by several proteins including synaptotagmin (Ca2+-binding protein attached to the vesicle) and the SNARE (Soluble NSF Attachment Protein REceptor) fusion machinery consisting of the vesicle SNARE (synaptobrevin) and the target membrane SNAREs (SNAP-25 and syntaxin). Upon action potential arrival and subsequent transient Ca2+ influx, Ca2+ -binds to synaptotagmin triggering the rearrangement of the SNARE complex and enabling membrane fusion within microseconds after Ca2+ entry.

The membrane fusion model of exocytosis is so far lacking detailed structural confirmation (McMahon et al., 2010). Our aim is to do a time resolved structural analysis of vesicle exocytosis, in a close-to-native biological sample (ex-vivo). The method used is cryo-electron microscopy (cryo-EM), that makes it possible to observe biological samples fully hydrated without the need for potentially damaging preparation steps such as chemical fixation, dehydration, and heavy metal staining, hence, producing fewer artefacts (Dubochet and Sartori-Blanc, 2001).

Therefore, in this study rat synaptosomes are used to investigate exocytosis. Using cryo-fluorescence microscopy we are able to localize fusion events directly on the electron-microscope grid, to later relocalize the same region much faster in cryo-EM, followed by subsequent analysis of the acquired tomograms by 3D reconstruction.

Confirming and complementing the biochemical data of synaptic vesicle exocytosis by structural analysis is an important step for further analysis of hypo- and hyperactivity of neurotransmitter release as well as for our general understanding concerning this process.

## C2 Recruitment of CaV3.2 channels through GluN2C-containing NMDA receptors in the nucleus Reticularis thalami

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Rhythmic burst discharge of nucleus Reticularis thalami (nRt) neurons plays a central role in the generation of synchronous thalamocortical oscillations during sleep and is primarily mediated by voltage-gated low-threshold T-type Ca2+ channels of the CaV3.3 subtype (Astori e al., 2011). The contribution of the co-expressed CaV3.2 subtype (Talley et al., 1999) to sleep rhythms has not been ascertained. To examine the role of T-channel subtypes during sustained thalamocortical synaptic activity typical of some sleep oscillations, we measured low-threshold T-currents in nRt cells under conditions of enhanced ambient glutamate levels. Patch-clamp recordings from nRt cells in brain slices of 3-week-old wild-type (WT) mice revealed that acute blockade of glutamate transporters with TBOA (100 µM) induced an increase in T-current amplitude (increase above baseline: 60 ± 13 %, n = 5, $p < 0.01$). This augmentation was prevented by blockade of NMDA receptors (NMDARs) with D,L-APV (100 µM) and mimicked by brief bath application of NMDA (30 µM) (6 ± 6 %, n = 5, $p > 0.05$ and 97 ± 24 %, n = 7, $p < 0.01$, respectively). GluN2C- containing NMDARs were required, as indicated by the lack of NMDA-induced changes in the presence of the GluN2C/D antagonist PPDA (500 nM, 11 ± 4 %, n = 7, $p > 0.05$). Interestingly, T-current augmentation persisted in CaV3.3-/- mice (103 ± 9 %, n = 5, $p < 0.01$), but was suppressed in CaV3.2-/- mice (6 ± 5 %, n = 10, $p > 0.05$). These results indicate a possible glutamatergic mechanism that controls CaV3.2 channel recruitment through GluN2C-NMDAR-mediated activation. Notably, GluN2C-NMDARs are expressed at both cortical and thalamic synapses onto nRt: PPDA reduced the amplitude of NMDA-EPSCs evoked at both inputs (cortical: 56 ± 6 % of control, n = 4, $p < 0.01$; thalamic: 72 ± 7 % of control, n = 7, $p < 0.05$). Thus, it is likely that sustained thalamocortical synaptic activity, e.g. during repetitive discharges such as sleep spindles, affects nRt excitability by recruiting CaV3.2 channels. We are currently testing this hypothesis by means of optogenetic stimulation of glutamatergic synapses onto nRt.
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## C3 GABA bidirectionally controls AP firing in newly generated hippocampal granule cells

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Newly generated young hippocampal granule cells in the adult brain receive depolarizing GABAergic synaptic inputs, which were shown to be important for their development and functional maturation. Whether activation of GABAergic synapses can evoke action potential (AP) firing in newly generated granule cells is yet unknown. To identify the young neurons in the adult brain, we used transgenic mice expressing the red fluorescent protein DsRed under the control of the doublecortin (DCX)- promoter. Perforated-patch recordings (gramicidin) revealed that the reversal potential of GABAergic synaptic currents is substantially more positive in DCX-expressing young neurons (-34.2±2.1mV) as compared to mature granule cells (-71.9±2.9mV). Coincidentally activated with depolarizing current injections or glutamatergic synaptic transmission, GABAergic synapses generated a biphasic response pattern. GABAergic synaptic currents were indeed able to excite AP firing in young granule cells within a conductance window between ~0.5 and 6nS. Larger GABAergic inputs, however, effectively blocked AP firing via shunting inhibition, which might be important to protect the young cells from over excitation. Synaptic GABAergic transmission was fully blocked by 10µM gabazine, whereas a half maximal concentration (0.2µM) increased AP firing at high stimulation intensities, showing that both AP boosting and shunting inhibition are mediated by a GABA-A receptor mediated chloride conductance. Taken together, we show that GABAergic synaptic inputs in newly generated young granule cells can dynamically support either AP generation or shunting inhibition dependent on hippocampal network activity.
Supported by Swiss National Science Foundation (SNSF)

## C4 Soluble factors derived from endothelial progenitors promote brain mi-crovascular cell viability

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Introduction: Soluble factors secreted by stem/progenitor cells play a pivotal role in tissue repair. In the present study we investigated whether paracrine factors derived from cultured endothelial progenitor cells (EPC) may support brain endothelial cell viability. Moreover, we addressed the type of factors and signaling pathways that may be involved.

Methods: Cultures from rat brain endothelial cells (rBCEC4) were incubated with EPC-derived conditioned medium (EPC-CM). rBCEC4 cell viability was assessed using the Presto Blue assay. Serial dilution (10%-20%-50%), molecular weight fractionation (2KDa, 30KDa and 100KDa) and heat inactivation experiments were performed to narrow down the key effectors of EPC-CM- mediated effects on rBCEC4 cells. The specific AKT inhibitor LY294002 and the ERK inhibitor PD98059 were used to analyze the involvement of these two signaling pathways in the transduction of the effects of EPC-CM.

Results: rBCEC4 cell viability significantly increased following incubation with EPC-CM. The capacity to support rBCEC4 cell viability was maintained up to final concentration of 20% EPC-CM. Importantly, the effect of EPC-CM was abolished by heat inactivation and molecular weight fractionation. Both, inhibition of the AKT and the ERK pathway suppressed the EPC-CM dependent increase of rBCEC4 cell via-bility.

Conclusion: In sum, our findings demonstrate that EPC derived paracrine factors substantially promote viability of brain microvascular cells by activating AKT and ERK signaling cascades. In addition, the activity of EPC-CM to support brain microvascular cell viability apparently relies on the concerted action of a variety of proteinaceous factors with different molecular weights.

## C5 Interaction between serotonin 1A and 2A receptor subtypes in neuronal cells

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Serotonin 1A (5-HT1A) and 2A (5-HT2A) receptors are serotonin receptor subtypes implicated in psychiatric disorders, including anxiety, depression, schizophrenia and obsessive-compulsive disorder. 5-HT1A and 5-HT2A activation may have counteractive effects on downstream signaling molecules, including glycogen synthase kinase 3 and n-methyl-D-aspartate receptors. Functional interaction between 5-HT1A and 5-HT2A receptors has been suggested, but its molecular basis is not clarified. The aim of the current study was to gain insight in downstream targets involved in the interaction between 5-HT1A and 5-HT2A receptors. We confirmed HTR1A and HTR2A mRNA expression in rat cortical neurons and rat pheochromocytoma PC12 cells using qRT-PCR. The expression of the 5-HT1A and 5-HT2A receptors was further confirmed on the protein level with western blot. We used an antibody array that allows the simultaneous detection of 18 well-characterized signaling molecules when phosphorylated or cleaved to screen for downstream targets differentially regulated by 5-HT1A and 5-HT2A or involved in their interaction. Protein lysates from rat cortical neurons treated with vehicle, 1 µM of the 5-HT2A agonist DOI, 1 µM of the 5-HT1A agonist 8-OH-DPAT, or pretreated with 1 µM 8-OH-DPAT before treatment with 1 µM DOI were analysed. The array results showed phosphorylation of the extracellular signal-regulated kinase (Erk1/2) at Thr202/Tyr204 and the stress- activated protein kinase/Jun-amino-terminal kinase (SAPK/JNK) at Thr183/Tyr185 as molecular modifications that are increased by DOI treatment and decreased towards baseline by pretreatment with 8-OH-DPAT. Our results suggest phosphorylation of ERK and JNK as downstream targets of 5-HT1A and 5-HT2A receptors that may be involved in their interaction.

## C6 Notch/RBPJ Mediated Activation of pAkt Signaling Pathway Following Seizures Results in Neurodegeneration via Erroneous Cell-Cycle Re-entry

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Neuronal demise is a principal cause of irreversible behavioral impairments associated with several neurodegenerative disorders. Although these disorders do not necessarily share the same pathophysiology, they all ultimately result in neurodegeneration in specific neuronal circuits. Hence, it is tempting to speculate that various neurodegenerative disorders may finally impinge upon common molecular pathways that result in neurodegeneration.

Our group previously showed that Notch signaling is aberrantly induced in the mouse model of stroke and likely contributes to cell death. We have found that kainate-induced excitotoxicity causes S-phase reentry in hippocampal CA-field neurons, which also show nuclear expression of Notch-1. Furthermore, kainate-induced excitotoxicity is associated with a concomitant Notch- dependent phosphorylation of AKT and its substrate GSK3. The phosphorylation-induced inactivation of GSK3 is associated with decreased phosphorylation of CyclinD1. This results in cell cycle re-entry through the activation of CyclinD-Rb-E2F1 axis. RBP-JK conditional knockout (RBPJKcKO) mice, which lack canonical Notch signaling, show marked resistance to neurodegeneration following kainate-induced excitotoxicity. We also find that pharmacological blockade of both pAKT as well as CyclinD1 activity in wild type mice confers resistance against KA induced neurotoxicity. Thus, we postulate that excitotoxicity causes neurodegeneration by aberrant cell cycle initiation through pAkt signaling pathway in a Notch-dependent manner. Indeed, studies on postmortem specimens from patients with Alzheimer's disease have shown upregulation of Notch1 as well as increase in phosphorylation of Akt and Gsk3, along with the upregulation of cell cycle related genes in degenerating neurons.

These studies will help us unravel the unique mechanisms of neuronal death involving cell cycle re-entry and pave a way to identify common therapeutic targets to prevent neurodegeneration and associated behavioral alterations.

## C7 Activity-dependent splice site selection and differential protein half-life distinguish CB isoform function at GABAergic synapses

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Collybistin (CB) is a brain specific RhoGEF with Cdc42 and GTP-TC10 as known substrates. As a RhoGEF, CB contains a Dbl- homology domain (DH) and a neighboring pleckstrin-homology domain (PH). At GABAergic synapses CB interacts with gephyrin, a scaffolding protein, and neuroligin2, a transmembrane synaptic protein, playing an essential role in their maintenance and function. In rat, three major splice isoforms (CB1-CB3) are transcribed from the gene Arhgef9, differing in their C-terminus and by the presence/absence of a src homology domain 3 (SH3) in their N-terminus. In this study we unraveled a mechanism for inhibitory synapses to respond to changes in network activity. Using a combination of biochemistry and cell biology, we dissected the role of the CB splice variants CB1SH3+, CB1SH3-, CB2SH3+ and CB2SH3- in regulating gephyrin clustering at GABAergic synapses. Quantitative RT-PCR (qRT-PCR) analysis showed that post-transcriptional regulation of CB splicing, with reduced splice site selection of CB1 and CB3 upon chronic depolarization of cultured neurons by KCl. This activity-dependent splice site selection could be specifically prevented by the CamK inhibitor Sto609. In addition, using a heterologous expression system, we demonstrate that CB1 and CB2 splice isoforms exhibit significant differences in their protein half-life. By identifying and mutating putative ubiquitin sites on the C-terminus of CB we uncovered a distinct regulatory mechanism for each of the isoforms tested. Finally, we show in primary neuronal cultures that mRNA of CB isoforms are dendritically transported, suggestive of local protein translation at inhibitory synapses. Our results offer a novel mechanism of plasticity changes at GABAergic synapses.

### C8 Optogenetic and electrophysiological dissection of the oxytocin brain circuitry of social behavior: differential effects of oxytocin in the medial and central amygdala as a basis for its role as a social molecule

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The 9 amino acid neuropeptide oxytocin (OT) appears to play an important role in social behavior. This could be mediated through OT-induced decreases in fear in combination with increases in affiliative behavior that are mediated through OT receptors in respectively the central (CeA) and medial (MeA) nuclei of the amygdala. Interestingly, electrophysiological in vitro studies have shown that neurons in the MeA are differently sensitive to OT compared to neurons in the CeA and more rapidly desensitize in the CeA. An imbalance between both OT signaling systems may underlie certain psychiatric disorders such as autism.
We here hypothesize that differences in intracellular signaling, mediated by distinct G proteins and associated recruitment of beta-arrestin, underlie the observed differences in sensitivities and desensitization to OT and OT-antagonists. To test our hypothesis, we compared increases in spiking activity measured by cell-attached patch clamp in CeA and MeA following 3-4 consecutive applications of oxytocin agonists and blocking effects by the G-protein specific OT antagonist Atosiban. Our preliminary results showed responses in 29% of CeA neurons to first TGOT application that subsequently rapidly desensitized. In the MeA 18% of neurons responded that exhibited significantly less desensitization upon consecutive applications. Responses in the MeA could selectively be blocked by Atosiban. These findings suggest that different G proteins in the CeA and MeA underlie the effects of OT signaling. In view of various pharmacological tools that can specifically affect distinct G proteins, our findings open up new insights into the possibilities to modulate OT signaling by more precisely targeted pharmacological therapies.

## D. Molecular and Cellular Mechanisms: Learning and Memory

### D1 Self-supervised learning of neural integrator networks

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Many functions of the brain require information to be kept or accumulated over long timescales, such as storing the current position of the eyes or accumulating evidence in a decision making process. The fact that a single neuron is very forgetful (~10ms memory) suggests that there must exist neural structures in the brain which can keep information for much longer timescales.
Although various neuronal recordings suggest the existence of such integrator networks, we still have no profound understanding about how they integrate and how they are formed. In fact, to achieve a stable integration, a fine tuning of the recurrent weight matrix (< 0.5% accuracy) is required, or additional stabilization mechanisms have to be introduced.
Here we consider a different approach to obtain stable neural integrators. Instead of imposing a specific wiring matrix to a neural network, we use a self-supervised learning paradigm for the feedforward and recurrent synapses projecting to the dendrites of two-compartment model neurons. The activity of these neurons are shaped by somatic teacher input, and the dendritic input learns to reproduce the somatic firing. The neurons are trained by projecting the derivative of a signal to the dendrite, and the original signal to the soma. After learning, the original signal is successfully reproduced from its derivative projected to the dendrite. Hence, the neurons learned to temporally integrate the dendritic input and represent this integral by the instantaneous somatic firing rate. This self-

supervised learning paradigm forms stable neural integrators with a minimal number of neurons (~200) using only AMPA conductances. The plasticity paradigm represents a candidate for a biologically plausible learning in a recurrent network.

## D2 Perisynaptic astrocytic processes are plastic structures contributing to learning and memory mechanisms

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Learning mechanisms in the central nervous system are associated with a rewiring of excitatory networks and the selective stabilization of synapses. Here we reveal an important contribution of perisynaptic astrocytic processes (PAPs) to these mechanisms. We found that hippocampal PAPs show extensive structural plasticity that is regulated by synaptic activity through astrocytic metabotropic receptors and intracellular calcium signaling. Synaptic activation that induces long-term potentiation caused a transient increase in PAP motility followed by their stabilization and an enhanced astrocytic coverage of the synapse. Selective activation of calcium signals in individual PAPs using two-photon flash photolysis reproduced these effects and determined spine stability. In vivo imaging in the somatosensory cortex revealed a similar PAP motility that was predictive of spine stability. Activity-dependent dynamic restructuring of PAPs may thus play an important role in memory mechanisms by enabling learning-induced synapse stabilization.

## D3 Regulation of microRNAs by protein phosphatase 1 in memory formation

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Emerging evidence suggests that microRNAs (miRNAs) contribute to the regulation of neuronal circuits involved in synaptic plasticity and memory formation. Our previous results have shown that protein phosphatase 1 (PP1) is a molecular constraint on memory formation. Inhibition of nuclear PP1 parallels the effect of training in a hippocampus-dependent memory task involving novel object recognition. We investigated whether PP1 exerts its regulatory effect on memory formation by modulating the expression of miRNAs. We conducted a deep-sequencing screen on mouse hippocampal miRNAs using a transgenic mouse model with improved memory performance resulting from inhibition of nuclear PP1 (NIPP1) in the adult brain. The results show that specific miRNAs are differentially expressed in NIPP1 mice, and that the same miRNAs are similarly differentially regulated after training in control mice. We further show that PP1 regulates the biogenesis of these miRNAs, and that their over-expression in the mouse hippocampus enhances long-term memory. This work provides evidence for the involvement of PP1 in the regulation of miRNAs in memory formation.

## D4 Synaptic integration in CA1 pyramidal neurons is controlled by dendritic GABAA 5 subunit- containing receptors

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Alpha5-containing GABAA receptors (5-GABAR) have been implicated in tonic inhibition, while their contribution to phasic synaptic inhibition remains more controversial. Recently, the 5-selective negative allosteric modulator (NAM) RO4938581 was shown to increase synaptic plasticity and improve spatial learning in a mouse model of Down syndrome (Martinez-Cue et al., 2013). Although this treatment has been suggested to rectify the over-inhibition found in Down syndrome, the precise cellular mechanisms remain obscure. Therefore, we investigated the effect of RO4938581 on individual hippocampal neurons in mouse brain slices. Tonic inhibition was evoked by bath-application of 5 µM GABA in the presence of 25 µM AP5 and 10 µM CNQX. Application of the 5-NAM (3 µM) reduced the GABA-dependent tonic currents (~25 pA) by about 25% in both granule cells and CA1 pyramidal neurons. To study phasic inhibition, inhibitory postsynaptic currents (IPSCs) were evoked by stimulating locally in the dendritic layer or close to the soma of CA1 pyramidal neurons. Slow dendritic IPSCs evoked in stratum lacunosum moleculare were significantly reduced to 64.4 ±14.4% after the application of 1M 5-NAM. In contrast, there was no reduction of somatic IPSCs evoked in stratum pyramidale. In the absence of glutamate receptor blockers, the addition of the 5-NAM (1 µM) increased postsynaptic potentials evoked by stimulating in the dendritic layer by 42.8±11.9%. These results point to increased postsynaptic integration after 5-NAM as the principle mechanism that may underlie enhanced synaptic plasticity in the previous studies.

## D5 DNA hydroxymethylation: a novel epigenetic mark important for memory formation

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A tight regulation of gene transcription is critical for the formation of long-term memory (LTM). Epigenetic mechanisms such as DNA methylation, histone posttranslational modifications and RNA interference by non-coding RNAs such as microRNAs, are important regulators of gene transcription that in the brain, have recently been implicated in memory formation. Methylated cytosine (5-mC), a form of DNA methylation in mammals, is present on most genes and can be converted into 5- hydroxymethylcytosine (5-hmC) by TET-family proteins (TET1, 2 and 3). Although 5-hmC was initially considered as a by- product of 5-mC, its high level in many tissues including the developing and adult brain suggested that it is an epigenetic mark on its own that may also regulate gene expression. The goal of this project was to determine whether 5-hmC is associated with genes implicated in memory formation in the adult brain and if so, whether TETs contribute to its control. We examined this possibility by measuring 5-hmC and TETs expression after memory formation. Using contextual fear conditioning (CFC), we observed that 5-hmC is differentially modulated at specific genes in the adult mouse hippocampus after training, and that this modulation correlates with a change in TETs expression. CFC also altered miRNA expression and affected miRNAs family with complementary sites to TETs 3'UTRs. These findings support a role for TET proteins in the modulation of DNA hydroxymethylation associated with memory formation in the adult hippocampus, and newly suggest the implication of miRNAs.

## D6 Physiology and ion channel expression of axons of amygdala projection neurons

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Axons are the principal elements of neuronal signal generation and propagation in the brain. Despite this central function, our knowledge of axonal physiology originates mainly from classical studies of peripheral and cranial nerves, which is typically generalized to the CNS. However, there is a growing body of evidence demonstrating that CNS axons are highly diverse between various brain areas with remarkable functional properties that influence neuronal output and signal transmission (Debanne et al., 2011). Most of these studies were performed in the cortex, hippocampus, cerebellum or auditory brain stem, whereas virtually nothing is known about the physiological function of axons of amygdala projection neurons - pyramidal-like neurons which are critically involved in emotional learning and processing. Here we use a combination of direct axonal electrophysiological recordings and two-photon Ca2+ imaging to characterize the features of axonal action potential initiation, transmission and activity-dependent Ca2+ signaling in basolateral amygdala projection neurons. In addition, we investigated their axonal ion channel distribution and myelination pattern using immunohistochemistry and confocal imaging. These data will not only increase the knowledge of the physiological variety of CNS axon function, but also provide further insight into the functional properties of amygdala projection neurons, which are potential drug targets for the treatment of anxiety disorders.

Debanne et al.. Axon physiology. Physiol Rev. 91(2): 555-602. 2011

## D7 Early traumatic stress alters transcriptional profile, synaptic plasticity and memory performance across generations in mice

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Traumatic stress experienced early in life constitutes a major risk factor for the development of behavioral and emotional disorders and for cognitive impairment later in life. Stress-related pathologies often have a strong heritable component, and epigenetic factors are thought to play a role in disease transmission. Previous work from our laboratory has demonstrated transmission of trauma-induced behavioral and molecular alterations across subsequent generations. We hypothesized that traumatic stress exposure would alter transcriptional processes in the brain across generations. To test this hypothesis, we exposed newborn pups to unpredictable maternal separation combined with unpredictable maternal stress (MSUS) during early postnatal life, a manipulation that leads to cognitive impairment and depressive-like behaviors in adult animals. We then conducted unbiased transcriptomic analyses in the hippocampus of the offspring. Gene set enrichment analyses revealed network-wide effects of MSUS on gene expression at rest, but also following an acute stress challenge. Specifically, pathways involved in synaptic plasticity showed reduced activity in the offspring of mice subjected to MSUS. Consistently, several forms of synaptic plasticity were altered in the mice exposed to MSUS. Long-term potentiation (LTP) was severely reduced both in male mice exposed to MSUS and the F2 offspring. The profound impairment in the offspring was observed across a broad range of stimulation intensities and persisted after cross-fostering, indicating that transmission likely occurred through the male germline, independent of maternal care. In agreement with the observed alterations in gene expression and synaptic plasticity, long-term memory was also impaired in MSUS fathers and their F2 offspring. These results suggest that paternal early life experience can have a long-lasting impact on synaptic plasticity and memory performance in the offspring.

## D8 The relationship between PSD-95 clustering and synapse stability

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The main substrates for structural neural network plasticity are synapses. Evidence for structural remodelling of synaptic circuits has mostly been based on static assessments of synapses using electron microscopy (EM) or on time-lapse imaging of dendritic spines and axonal boutons, which may function as proxies for synapses. It has been shown that, in the adult somatosensory cortex, the majority of the spines are stable. However some spines appear and disappear over time. Moreover, some of the new spines stabilize, and the number of new spines undergoing stabilization can be increased by learning and changes in sensory experience. Retrospective EM analysis of imaged spines has shown that many newly formed spines do not bear a morphologically defined synapse, and those new spines that contain synapses mature slowly. These data suggest that the outgrowth of spines and the stabilization of spines with synapses are regulated by different processes. However, the temporal relationship remains unknown. Here we probed in real time in vivo, the dynamics of excitatory synapses using 2-photon laser scanning microscopy (2PLSM) of GFP- tagged postsynaptic density protein 95 (PSD-95) in L2/3 pyramidal cells. Using retrospective EM we determined that PSD-95- GFP puncta as seen with 2PLSM reliably represented synapses. Spine head size and PSD-95-GFP levels co-varied over time suggesting a continuous change in synapse strength. The majority of newly formed spines did not acquire PSD-95-GFP puncta and rarely survived for more than 1 day. Although PSD-95 incorporation increased spine life times, the majority of the spines with puncta did not stabilize for long periods of time. Similarly, although the majority of persistent spines that were destined to be pruned lost their PSD concomitantly, they often showed reduced or fluctuating PSD-95-GFP levels well before the actual disappearance. Altogether, our results indicate that transient spines incorporating PSD-95 may serve as short-lived synaptic contacts, and that PSD-95-GFP levels and stability are reliable measures of synapse dynamics in vivo.

## D9 Self-stimulation of VTA DA neurons is sufficient to mimic key features of addiction in mice

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Addictive drugs increase dopamine (DA) concentration in the ventral tegmental area (VTA) and its target areas, such as the nucleus accumbens NAc and pre-frontal cortex (PFC), which induces drug-adaptive behavior.
However, addictive drugs also have additional pharmacologic targets. Evidence that increased DA in the VTA is sufficient to evoke the pathological synaptic and behavioral changes observed in addiction is still lacking. Here, we show that blue-light self- stimulation of VTA dopaminergic neurons infected with channel rhodopsin evoked synaptic plasticity and adaptive behavior similar to cocaine self-administration.
First, stimulation of DA neurons reinforced lever pressing and was followed by cue-induced reward seeking after a several weeks of abstinence. In parallel we observed a strengthening of excitatory synapses onto dopamine D1 receptor-expressing neurons (D1R-MSN) of the nucleus accumbens.
Moreover, when self-stimulation was associated with punishment (brief electric shock), some animals showed a strong perseverance of responding, akin to drug-consumption despite the negative consequences. Resistance to punishment for both light and cocaine were correlated with a hypoexcitability of pyramidal neurons in the prelimbic cortex.
Together, these results show that self-stimulation of VTA DA neurons is sufficient to trigger key features of addiction.

## D10 Tameness selection impacts adult hippocampus neurogenesis along the septo-temporal axis in silver fox brain

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New neurons are continuously generated and functionally integrated in the adult hippocampal dentate gyrus of mammals. However, the function of adult hippocampal neurogenesis (AHN) remains debated. Diverging experimental outcomes might be associated with domestication-induced processes, or related to methodological variability. Recent evidence indicates that the hippocampus is not a homogeneous structure: the septal part is most likely associated with spatial learning and navigation, while the temporal part is associated with emotional functions.

In this report we compare AHN along the hippocampal septo-temporal axis of domesticated silver foxes selected for tameness to non-selected animals. We used design-based stereological method to estimate the numbers of proliferating cell (Ki67+) and young neurons (doublecortin+) in defined septal and temporal regions.

Significantly higher neurogenesis could be observed in the hippocampi of tame silver foxes compared to the non-selected animals. Interestingly, most of the differences were found in the polymorphic/hilar region of the dentate gyrus. Region-specific cell quantification normalized by the local granule cell number showed a higher neurogenesis in the temporal hippocampus in both tame and non-selected fox brains. Regionally normalized results also reveal higher septal hippocampal neurogenesis in tame foxes.

In conclusion, our data link the up-regulation of neurogenesis with tameness-selected domestication and also confirm the regional heterogeneity of the mammalian hippocampus. This distinction is mostly observed in the polymorphic/hilar region of the dentate gyrus, especially in the septal hippocampus. These results provide important information for understanding the specific function of adult hippocampal neurogenesis along the septo-temporal hippocampal axis.

## D11 Deep brain stimulation reverses behavioural sensitization to cocaine

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Exposure to drugs of abuse, such as cocaine, induces characteristic forms of synaptic plasticity, for instance a potentiation of glutamatergic inputs onto medium spiny neurons of the nucleus accumbens (NAc). One behavioral correlate of this plasticity is locomotor sensitization, a phenomenon in which repeated exposure to equivalent doses of cocaine induces progressive increases in locomotor activity. Previously, our laboratory has demonstrated that depotentiating the projection from the medial prefrontal cortex (mPFC) to the NAc using optogenetic stimulation delivered at low frequencies (13 Hz) restores normal synaptic transmission and abolished locomotor sensitization to cocaine. Deep brain stimulation (DBS) is a surgical therapy used primarily for movement disorders, in which electric current is passed through electrodes implanted into specific brain nuclei. In this study, we sought to reverse locomotor sensitization using DBS applied to the fiber bundle of excitatory projections originating in the mPFC and targeting the NAc shell. We found that classical DBS protocols (high frequency: 130Hz, 100A) effectively decreased the locomotor response to cocaine. However, this effect was transient and lasted less than four hours after the cessation of DBS. In line with these behavioral observations, the cocaine-induced enhancement of excitatory inputs onto MSNs was unchanged, as inferred by measuring the AMPA:NMDA ratio ex vivo 24 hours following the cessation of DBS. We then attempted to test a DBS at 13Hz for 10 minutes, a stimulation protocol shown to reverse the strength of excitatory inputs onto MSNs. However, given that the 13Hz protocol is dependent on mGluR activation, and that signaling through dopamine D1-

receptors in MSNs opposes mGluR signaling, we hypothesized that D1 antagonism may be necessary to unmask a depotentiation onto MSNs. Indeed, when we administered the D1 antagonist SCH23390 (0.1mg/kg, i.p.) in conjunction with DBS, cocaine sensitization was reduced. This reduction was evident 24 hours after application of DBS. Taken together, our results provide a proof of principle that combined with pharmacology, DBS may be used to reverse to cocaine-induced locomotor sensitization and synaptic plasticity.

## D12 Cocaine-evoked plasticity at susceptible accumbal synapses controls relapse

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Relapse to drug use even after a long period of abstinence is a cardinal feature of drug addiction. Here we established causality between drug-evoked synaptic plasticity and behavioral components that underlie relapse. After abstinence from cocaine self- administration in mice, we found that excitatory transmission at basolateral amygdala (BLA), medial prefrontal cortex (mPFC) or ventral hippocampus (vHipp) inputs onto D1- or D2-receptor-medium spiny neurons (D1R- or D2R-MSNs) in the nucleus accumbens is altered in different ways. Specifically, rectifying AMPA receptor transmission, indicating the presence of GluA-2 lacking AMPARs, and a reduced AMPAR/NMDAR ratio was found only at mPFC to D1R-MSN synapses. In contrast, at vHipp to D1R-MSN synapses the AMPAR/NMDAR ratio was increased while no change occurred at BLA to D1R-MSNs. In this same paradigm, excitatory synapses onto D2R-MSNs were not modified following abstinence from cocaine. To provide causality between these drug-evoked changes in plasticity and behavior, we used optogenetics to restore basal transmission at both mPFC and vHipp synapses, which was sufficient to abolish cue-induced seeking. Removal of cocaine evoked plasticity only at mPFC or vHipp synapses resulted in impaired action-outcome selection or vigor of responding, respectively. Thus, we identify “susceptible synapses” in the NAc through which cocaine alters information integration to permit relapse. Our findings may inspire novel approaches to determine causal links between synaptic and behavioral adaptations.

## D13 Cellular mechanisms of long-term depression at neocortical L4-L2/3 synapses in juvenile rats

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Spike-timing dependent depression at L4-L2/3 synapses in the developing somatosensory cortex depends on retrograde endocannabinoid signaling via astrocytes. We found that the activation of astrocytic cannabinoid receptors leads to increased calcium activity and astrocytic glutamate release, which in turn activates presynaptic NMDA receptors during the induction of spike timing-dependent depression. Furthermore, direct activation of astrocytes by depolarization paired with presynaptic activity alone also results in LTD. This form of astrocyte mediated LTD shares the same signaling cascades as timing- dependent LTD and also requires activation of presynaptic NMDA receptors. However, the functional role of presynaptic NMDA receptors in LTD induction is still elusive. Here we show preliminary results addressing this question. Using bath application of endocannabinoid receptor agonist together with selective blockade of calcium signaling in astrocytes we show that endocannabinoid-dependent astrocytic calcium signaling and the resulting release of glutamate onto presynaptic NMDA receptors is necessary and sufficient for the induction of LTD. This strengthens our hypothesis that presynaptic cannabinoid receptors are not involved in LTD, but presynaptic NMDA receptors are. We further present our optical imaging approach with which we plan to demonstrate how presynaptic NMDA receptors are specifically activated by astrocytic glutamate release. This would suggest that presynaptic NMDA receptors are shielded from synaptic glutamate release by neighboring astrocytes.

## D14 Analyses of sub-regional functions of the adult mouse hippocampus in memory formation by proteomic profiling

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The hippocampal formation is a brain structure important for higher-order brain functions, whose dorsal portion is particularly required for cognitive processes. It is characterized by two anatomically distinct regions, areas CA1 and CA3, which have similar pyramidal neurons, both needed for memory formation, but with distinct functional and morphological properties. The aim of this study is to determine what distinguishes hippocampus area CA1 from CA3 in the adult mouse brain at a proteome level during memory formation. Using iTRAQ, a high-throughput unbiased mass spectrometric method for quantitative proteomics, we identified different proteins in area CA1 and CA3, which are significantly up- or down-regulated 4 or 24 hours after an object location memory task in at least one of these areas. Using a targeted proteomic approach, we are currently examining the expression profile of these proteins across time in relation to different forms of memory and in pathological conditions. Ultimately, these analyses are expected to identify the proteome associated with the specific contribution of area CA1 and/or CA3 to memory formation and its alteration.

# E. Neural Excitability Synapses: Functional Aspects

## E1 RIM-Binding Protein Promotes Homeostatic Modulation of Neurotransmitter Release and Resupply of Release-Ready Vesicles

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Stable neural function is a prerequisite for robust animal behavior. However, the molecular mechanisms conferring robustness to neural activity are poorly understood. At the Drosophila neuromuscular junction (NMJ), synaptic efficacy is stabilized through homeostatic control of neurotransmitter release. This form of synaptic plasticity is initiated by inhibition of postsynaptic glutamate receptor function and induces a homeostatic increase in presynaptic calcium influx and release-ready vesicle number. RIM-Binding Proteins (RBPs) were recently demonstrated to be crucial for normal clustering of presynaptic calcium channels, calcium influx, and neurotransmitter release probability under baseline conditions. Here we demonstrate that RBP is essential for homeostatic modulation of neurotransmitter release at the Drosophila NMJ. Specifically, RBP is necessary for the homeostatic potentiation of presynaptic calcium influx and expansion of the readily-releasable vesicle pool. We then examine how RBP controls vesicle release at baseline and during homeostatic plasticity. In rbp mutants we document a ~10-fold decrease in the apparent calcium sensitivity of release that can be attributed to 1) impaired calcium influx, 2) looser coupling between synaptic vesicles and calcium influx and 3) limited access to the readily-releasable vesicle pool, which contains the same absolute number of vesicles as in wild type. Remarkably, loss of RBP also dramatically slows (~4-fold) the replenishment rate of high release probability vesicles following a stimulus train. We propose that RBP coordinately controls high release probability vesicles and presynaptic calcium influx to stabilize synaptic efficacy during baseline transmission and homeostatic synaptic plasticity.

## E2 Localization of glycinergic neurons selectively activated during paradoxical sleep in the rat: their potential role in the control of muscle atonia

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During paradoxical sleep (PS), somatic motoneurons are inhibited causing a tone loss in the whole skeletal musculature, a motor event characteristic of this sleep state. As revealed by intracellular recordings of masseter and lumbar motoneurons in the cat, glycine is the main inhibitory neurotransmitter involved in their sustained hyperpolarization during PS. In our current functional model, glutamatergic PS-on neurons of the pontine sublaterodorsal nucleus (SLD) are responsible for the genesis of PS atonia by means of their excitatory projections descending to glycinergic premotoneurons. However, the exact location within the brainstem and/or spinal cord of the glycinergic premotoneurons selectively activated by glutamatergic SLD excitation during PS still remains a matter of debate. To bridge this gap, we have implanted for polysomnigraphic recordings (EEG and EMG) 4 experimental groups of rats: 1) control (PSC); 2) PS deprived during 72h with the flower pot technique (PSD, n=4); 3) allowed to recover for 150 minutes of such deprivation during which they experienced 40% of PS (PSR, n=4); and 4) forced to walk for 2h (STEP, n=4). Ten days before PS deprivation, PSR rats were submitted to a retrograde tracer Fluorogold (FG) injection into the ventral spinal cord at T13-L1 levels. Pons, brainstem and spinal cord sections were then processed for double labeling combining immunohistochemistry of Fos (used as a marker of neuronal activity) with non-radioactive in situ hybridization of GlyT2 mRNA (the neuronal glycine reuptake transporter). Sections from PSR rats were also submitted to Fos/FG double immunostaining. At the brainstem, Fos+/GlyT2+ neurons were quite exclusively observed in PSR rats, with the highest number of double-labeled cells detected within the raphe magnus (RMG), alfa (Gi), ventral gigantocellular (GiV) and lateral paragigantocellular (LPGi) medullary nuclei, where 80% of Fos+ neurons expressed GlyT2. Within the lumbar cord, occasional Fos+/GlyT2+ neurons were seen in PSC, PSD and PSR rats while they were numerous in STEP rats with a sustained locomotor activity prior to sacrifice. Finally, Fos/FG double immunostaining in PSR rats unravel that 45% of Fos+ neurons almost exclusively in GiV and less than 10% in SLD project to the ventral spinal cord. These results indicate that glycinergic neurons of GiV, selectively activated during PS and projecting directly to the spinal cord, hyperpolarize somatic motoneurons during PS. Our hypothesis is that during PS, SLD glutamatergic neurons excited the glycinergic neurons of GiV, who are responsible for the PS-specific hyperpolarization of spinal somatic motoneurons, causing muscle atonia.

## E3 Firing modes of dopamine neurons drive bidirectional GIRK channel plasticity

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G-protein coupled inwardly rectifying potassium (GIRK) channels contribute to the resting membrane potential of many neurons, including dopamine (DA) neurons in the ventral tegmental area (VTA). VTA DA neurons are bi-stable, firing in two modes; one characterized by bursts of action potentials, the other by tonic firing at a lower frequency. Here we provide evidence that the firing modes drive bi-directional plasticity of GIRK channel-mediated currents. In acute midbrain slices of mice, we observed that in vitro burst activation of VTA DA neurons potentiated GIRK currents whereas tonic firing depressed these currents. This plasticity was independent of the metabotropic receptor activating the GIRK channels, as GIRK channel directly activated by non-hydrolysable GTP were also potentiated. The plasticity of GIRK currents required NMDA receptor and CAMKII activations and involved protein trafficking through specific PDZ domains of GIRK2c and GIRK3 subunit isoforms. Prolonged tonic firing may thus enhance the probability to switch into burst-

firing mode, which then potentiates GIRK currents and favors the return to baseline. In conclusion, activity-dependent GIRK channel plasticity may represent a slow destabilization process favoring the switch between the two firing modes of VTA DA neurons.

## E4 Serotonergic modulation of whisker-evoked responses in the mouse barrel cortex

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Unbalanced serotonin production or sensitivity can lead to mood, appetite and sleep disorders, but also disturbs memory and cognitive functions. In the mouse cortex, cross-modal plasticity, i.e. map plasticity across different sensory modalities, is modulated by serotonin. This type of plasticity is thought to be important for optimization of sensory processing and implicit learning. In the adult sensory cortex, serotonin is released from raphe nuclei (RN) afferents and a large variety of serotonin receptors are present on cortical pyramidal neurons as well as on inhibitory interneurons. Our goal is to characterize the mechanisms that underlie the serotonin-mediated modulation of cortical plasticity. We use the mouse somatosensory barrel cortex as a model system. In a first set of experiments, we are studying the effect of serotonin release on sensory inputs from the whiskers to the somatosensory cortex. Using targeted expression of ChR-2 in RN neurons, we optically activate their projections to the cortex, while recording L2/3 pyramidal neuron responses in vivo (extracellular and whole cell recordings). Our data show that light-induced serotonin release can moderately modulate the rate of sensory-evoked action potentials and the amplitude of sensory-evoked local field potentials. In order to see how acute serotonin release modulates functional plasticity in the somatosensory cortex, we aim at combining these experiments with sensory-evoked LTP paradigms. In a separate set of experiments, we are studying the effect of sensory inputs from the whiskers to the RN. For this purpose we perform (a) extracellular recordings from RN neurons in vivo and (b) calcium imaging of RN projections to the somatosensory cortex, using targeted expression of the calcium indicator GCaMP-5 in RN neurons, in vivo. Our first data show that sensory stimulation can induce action potentials in RN neurons as well as Ca2+ responses in RN projections to the somatosensory cortex.

## E5 In vivo measurement of synaptic transmission between identified neurons in layer 2/3 mouse barrel cortex

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In order to obtain a causal and mechanistic understanding of how sensory information is processed in the neocortex, it is essential to measure the properties of synaptic transmission between neurons in living animals. Here, we use a combination of single-cell optogenetics and whole-cell electrophysiological recordings to control and record the in vivo activity of individual pre- and post-synaptic neurons. Two-photon targeted single-cell electroporation (Kitamura et al. 2008) is used to deliver DNA encoding channelrhodopsin-2 (ChR2) to a single excitatory neuron located in upper layer 2/3 of the mouse barrel cortex. After allowing sufficient time for ChR2 expression, the excitatory neuron can be optically driven to fire repetitive, reliable and time- locked single action potentials. Parvalbumin-expressing (PV) GABAergic neurons (identified genetically in PV-Cre/Lox-Stop- Lox-tdTomato transgenic mice) or somatostatin-expressing (SST) GABAergic neurons (identified genetically in SST-Cre/Lox-Stop-Lox-tdTomato transgenic mice) located in the vicinity of the ChR2-expressing neuron are then sequentially recorded in the whole-cell configuration while the ChR2-expressing neuron is optically stimulated to fire action potentials. Using this method, we found that: i) the synaptic connectivity rate from excitatory neurons is higher to PV neurons compared to SST neurons; ii) the unitary excitatory postsynaptic potential (uEPSP) amplitude is on average of similar size in PV and SST neurons; iii) the uEPSP kinetics is slower in SST neurons compared to PV neurons; and iv) synapses onto SST neurons show a strong short-term facilitation while synapses onto PV neurons show a significantly weaker short-term facilitation.

**E6** **Roles for group II metabotropic glutamate receptors in hippocampal LTP**

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It is well established that at Schaffer collateral synapses onto CA1 pyramidal cells (PCs), activation of group I metabotropic glutamate (mGlu) receptors induces LTD. However, previous studies have reported that application of ACPD, a mixed agonist at group I and group II mGlu receptors, induces LTP. Here we used field and whole-cell recordings in the CA1 region to investigate the specific contribution of group II mGlu receptors to synaptic plasticity. Pharmacological activation of group II mGlu receptors with the specific agonist LY354740 induced LTP within 10 minutes at Schaffer collateral synapses. This form of plasticity was NMDA receptor-dependent, but was not associated with changes in the paired pulse ratio or fiber volley amplitude, consistent with a postsynaptic site of expression. The intracellular transduction pathway requires activation of G proteins and protein kinase C. As group II mGlu receptors consist of two subtypes, mGlu2 and mGlu3, experiments were repeated with knockout mice. The results showed that LTP is mediated by mGlu2 receptors. Surprisingly, blocking GABAA receptors decreased potentiation by ~20%. Analysis of evoked IPSCs revealed that activation of group II mGluRs induces LTD in interneurons. Thus, our data indicates that this mechanism of disinhibition contributes to the enhanced synaptic responses in CA1 pyramidal cells mediated by group II mGlu receptors.

## F. Brain Metabolism and Homeostasis

**F1** **Altered microRNAs expression in synaptic plasticity in the adult mouse barrel cortex**

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In rodents, sensory experience alters the representation in layer IV of the barrel cortex. Excitatory and inhibitory interneurons, together with the astrocytic network, modify the functional representation in a very orchestral manner. Our group showed that continuous whisker stimulation in adult mice induces depression of neuronal responses and insertion of new inhibitory synapses on spines. This form of cortical plasticity is controlled by several gene regulatory mechanisms including the activation of genetic programs controlling the expression of microRNAs. To investigate the involvement of miRNAs in cortical plasticity, we selected four microRNAs known to be implicated in other forms of synaptic plasticity: miR-125b, miR-132, miR-137 and miR-138. After unilateral stimulation of three whiskers (C1 3) in the adult mouse, we compared the expression level of these miRNAs in stimulated and adjacent non-stimulated barrels using in situ hybridization with DIG-labeled LNA probes. Whisker stimulation increases the expression, of miR-132 after 3 hours of stimulation ($p=0.02$) and miR-137 ($p=0.03$; 24 hrs of stim.), whereas it reduces the level of miR-125b ($p=0.002$; 9 hrs of stim.). No significant difference was detected for miR-138. In addition to these quantitative comparisons, we combined microRNA in situ hybridization and immunolabeling using various markers for neurons and astrocytes. Confocal microscopic analysis showed a colocalization of miR-125b with GAD65/67 and Parvalbumin, miR-132 with GAD65/67 and Vglut2, miR-138 with Parvalbumin, Vglut1 and PSD95, and miR-137 with Vglut1, GS and S100ß. Stimulation alters the degree of colocalization in the stimulated barrel. For example, double labeling of miR-138 and PSD95 is 35% increased in the stimulated barrel as compared to the level of colocalization in the neighboring non- stimulated barrel. These results indicate that microRNAs have a potential role in sensory activity-dependent cortical plasticity in the adult mouse by acting specifically within the different cellular components of the neocortical circuit.

**F2** **Hydrocephalus caused by forebrain specific ferritin H inactivation in mice**

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To investigate the role of ferritin in the brain we generated mice with a forebrain specific ferritin H gene deletion. Absence of ferritin H in most cells of the forebrain including the choroid plexus of the lateral ventricles caused accumulation of cerebrospinal fluid in the ventricles and the subarachnoid space. No change in brain iron levels was observed.

## F3 Single cell lactate and glucose measurements in awake mice

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High resolution imaging in living animals could provide a deeper understanding of the cellular compartmentation of brain energy metabolism. So far, only a limited amount of data has been derived from in vivo neuroimaging studies. Furthermore, such studies were almost exclusively performed under anesthesia, which heavily alters physiological processes. The aim of the current study was 1.) to test if metabolic imaging using two-photon microscopy (2PM) with single cell resolution in combination with genetically encoded substrate sensors is feasible in the awake, head-fixed mouse and 2.) to examine the effects of isoflurane anesthesia on the signals.
In four mice, either the genetically encoded glucose sensor FLII12Pglu600µ6 (FLIP) or the lactate sensor Laconic (LAC) was injected into the somatosensory cortex. By using different promoters, cell-specific expression was ensured (short GFAP astrocytic; human Synapsin neuronal). Behavioral training started a few days after surgery. To reduce spontaneous motion artifacts, animals had to learn to tolerate head fixation without spontaneous motor activity. Animals were trained for at least three weeks before 2PM imaging sessions started. Sensory stimulation of 1 second duration did not lead to a change in astrocytic or neuronal substrate concentrations. Oral glucose administration led to a FLIP FRET signal increase in neurons and astrocytes. Surprisingly, isoflurane anesthesia resulted in an even higher increase of the signal compared to the awake state. Besides, isoflurane influenced both, glucose and lactate levels in the brain. However, lactate levels adapted much faster to a new brain state compared to glucose levels.
The presented experiments demonstrate the feasibility of awake 2PM imaging of different metabolites on a single cell level. The inhalational anesthetic isoflurane exhibits a large effect on intracellular substrate concentrations distinctly revealing the need for experiments in awake animals to measure unbiased physiological brain metabolism.

## G. Cognitive and Behavioral Neuroscience

### G1 A Task of Sustained Attention to Sound in Rat

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Background

The ability to follow behaviorally-relevant sources of sound is critical for animals' survival. In a typical noisy acoustic environment, sounds originating from different sources overlap in their temporal, spatial, and spectral dimensions. The cortical mechanism for extracting and tracking a chosen signal remains unknown. The aim of this work was to establish a behavioral paradigm for controlling spectra-spatial auditory attention in rats to be used during awake recordings of cortical activity.

Methods

Rats were trained to detect a 20 dB amplitude drop in a sequence of pure-tone pips (38 kHz) presented in parallel with a distractor stimulus of a different frequency (8 kHz). The target and distractor stimuli were presented from two different speakers, positioned at 90° separation in front of the head-fixed animal. Which speaker presented which frequency switched unpredictably from trial to trial. The animal had to indicate the side of the target frequency within a short time window of the amplitude drop by licking from a water spout on the corresponding side. To discourage impulsive behavior and ensure sustained attention, early responses triggered re-starting of the trial. The target and distractor frequencies were kept the same for a block of 50-100 trials and then were swapped, requiring the animal to shift its attention to the frequency it previously had to ignore. Following training, a four-shank electrode array (8 recording sites/shank) was chronically implanted in the left auditory cortex. Multi-unit and LFP activity was recorded while the animal performed the task.

Results

Rats were able to localize the side of the target stimulus with an accuracy of 85-90% when presented alone and ~65-70% when presented together with a distractor of the same volume. This is the first demonstration of successful pure tone localization for rodents in the head-fixed condition. A great heterogeneity of neural responses was recorded. Neurons separated by only 200 µm in cortical depth could vary by as much as two octaves in frequency tuning and 40 dB in amplitude selectivity. Responses to interleaved target-distractor pip sequences revealed stimulus-specific adaptation.

Conclusions

We have established a task for directing the animal's attention towards either of two competing auditory stimuli. By switching the target frequency within a session, the animal's internal state can be manipulated while keeping the external stimulation constant, a prerequisite for investigating the neural basis of attention.

### G2 Variability of manual dexterity performance in non-human primates (Macaca fascicularis): comparison of learning and plateau phases

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The goal of this study was to quantify the inter-individual and intra-individual variability of manual (digits) skill in adult macaque monkeys, over a motor learning phase and, later on, when motor skills were consolidated. The hypothesis is that several attributes of the stable manual dexterity performance can be predicted from learning characteristics. The behavioral data were collected from 20 adult Macaca fascicularis, derived from their dominant hand, defined as the hand exhibiting a better performance than the other. Two manual dexterity tasks were tested: (i) the "modified Brinkman board" task, consisting in the retrieval of food pellets placed in 50 slots in a board, using the

precision grip (opposition of the thumb and index finger); (ii) the "reach and grasp drawer" task, in which the grip force and the load force were continuously monitored while the monkey pulled a drawer against a resistance, before grasping a pellet inside the drawer. The hypothesis was verified for the performance of manual dexterity after consolidation, correlated with the initial score before learning. Motor habit, reflected by the temporal order of sequential movements executed in the modified Brinkman board task, was established very early during the learning phase. As mostly expected, motor learning led to an optimization of manual dexterity parameters, such as score, contact time, as well as a decrease in intra-individual variability. Overall, the data demonstrate the substantial inter-individual variability of manual dexterity in non-human primates, to be considered for further pre-clinical applications based on this animal model.

## G3 The impact of automatic alcohol associations on drinking behavior is moderated by baseline activation in the lateral prefrontal cortex

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Undue consumption of alcohol puts individuals at risk for chronic disease and injury. The social harm and the financial costs associated with excessive drinking are enormous not only for the affected individuals, but their social environments, and societies more generally. Paradoxically, most people drinking a lot of alcohol are well aware of the looming negative consequences and yet continue to drink, suggesting that other factors besides rational decision-making influence drinking behavior. Here, we use resting electroencephalography to measure objective and stable individual differences in baseline cortical activation and show that baseline activation in the right lateral prefrontal cortex (PFC) predicts individuals' self-reported drinking behavior. In addition, baseline cortical activation in this area works as a gatekeeper for the influence of automatic alcohol associations on drinking behavior: automatic alcohol associations are associated with drinking behavior for individuals with low, but not high, baseline cortical activation in the right lateral PFC. These findings reveal that a highly stable and specific neural marker can predict prolonged real-world alcohol consumption and modulate the impact of appetitive impulsive processes on this self-regulatory behavior.

## G4 Impartiality in humans is predicted by brain structure of dorsomedial prefrontal cortex

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The moral force of impartiality (i.e. the equal treatment of all human beings) is imperative for providing justice and fairness. Yet, in reality many people become partial during intergroup interactions; they demonstrate a preferential treatment of ingroup members and a discriminatory treatment of outgroup members. Some people, however, do not show this intergroup bias. The underlying sources of these inter-individual differences are poorly understood. Here we demonstrate that the larger the gray matter volume and thickness of the dorsomedial prefrontal cortex (DMPFC), the more individuals in the role of an uninvolved third-party impartially punish outgroup and ingroup perpetrators. Moreover, we show evidence for a possible mechanism that explains the impact of DMPFC's gray matter volume on impartiality, namely perspective-taking. Large gray matter volume of DMPFC seems to facilitate equal perspective-taking of all sides, which in turn leads to impartial behavior. This is the first evidence demonstrating that brain structure of the DMPFC constitutes an important source underlying an individual's propensity for impartiality.

## G5 BODY WEIGHT INFLUENCES THE INTERPLAY OF BRAIN DYNAMICS TO FOOD VIEWING AND GASTRIC HORMONE SECRETION

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Endocrine factors convey information about energy needs to brain regions involved in homeostatic control of food intake, but there is mounting evidence for influences on brain areas implicated in hedonic valuation, too. The extent to which endocrine factors interact with sensory and cognitive processes in differing food motivation states and whether individuals' body weight additionally impacts those processes is so far undetermined. Our study investigated the influence of weight on gut hormone secretion as well as associations with the spatio-temporal brain dynamics to food viewing in women ranging in BMI from 19-36 kg/m2 following an overnight fast and subsequent to food intake. BMI differentially influenced the scalp-surface global power of the electric field evoked by high-and low-energy food viewing from ~230ms in pre-prandial nutrition state. On the other hand, the food type viewed and BMI impacted the estimated neural source activity (by applying distributed linear inverse solutions and the LAURA regularization approach) in occipital and frontal regions already from ~100ms after image presentation in post-prandial state, the most prominent interactions being between responses to low-energy food viewing and BMI. Activity in these brain regions modulated by food type viewed and BMI was further correlated with peripheral blood measures of leptin and ghrelin, hormones known to convey food motivation signals along the gut-brain-axis. That is, motivation and body weight substantially influence visual food perception, altering activity in brain regions mediating sensory processing, but also valuation and decision-making. Gut hormone secretion is particularly associated with BMI- and motivation-dependent food valuation signals.

## G6 Bi-directional control of fear learning by amygdala interneurons

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Fear conditioning is one of the most powerful models to study the neuronal substrates of associative learning and the mechanisms of memory formation in the mammalian brain. The amygdala has been demonstrated to play a pivotal role in fear conditioning and other emotional learning paradigms, with a major focus classically been set to the study of excitatory neurons. However, interneurons are critical components of neuronal networks and inhibition plays an important role in shaping spatio- temporal patterns of network activity. The role of amygdala interneurons in fear conditioning, and especially of interneuron subtypes, is poorly understood. To unambiguously identify distinct subtypes of interneurons and to determine causal relationships between interneuron activity and behavior, we combined single unit recordings in behaving animals with a cell- type specific optogenetic approach. Recordings from optogenetically identified parvalbumin-expressing (PV+) interneurons during fear conditioning showed differential activity during CS (conditioned stimulus: tone) and US (unconditioned stimulus: foot-shock) exposure. Consistently, precisely timed optogenetic manipulations of the activity of PV+ interneurons during CS and/or US had differential effects on fear learning. Remarkably, manipulations of somatostatin-expressing (SOM+) interneurons caused effects opposite to PV+ manipulations. Taken together, our results strongly indicate that both PV+ and SOM+ interneurons play important, but differential roles in the acquisition of fear memories and suggest an interaction of PV+ with SOM+ interneurons.

## G7 A MATLAB based eye tracking control system using non-invasive helmet head restraint in the macaque

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Tracking eye position is vital for behavioral and neurophysiological investigations in systems and cognitive neuroscience. Infra- red camera systems are now available that can be used for eye tracking without the need to surgically implant magnetic search coils. These systems are generally employed using rigid head fixation in moneys, which maintains the eye in a constant position and facilitates eye tracking. Here, we investigate the use of non-rigid head fixation using a helmet that constrains only general head orientation and allows some freedom of movement. We present a MATLAB software solution to gather and process eye position data, present visual stimuli, interact with various devices, provide experimenter feedback and store data for offline analysis. Our software solution achieves excellent timing performance due to the use of data streaming, instead of the traditionally employed data storage, mode for processing analog eye position data. We present behavioral data from two monkeys, demonstrating that adequate performance levels can be achieved on a simple fixation paradigm and show how performance depends on parameters such as fixation window size. Our findings suggest that non-rigid head restraint can be employed for behavioral training and testing on a variety of gaze-dependent visual paradigms, reducing the need for rigid head restraint systems. While developed for macaque monkey, our system of course can work equally well for applications in human eye tracking where head constraint is undesirable

## G8 Simultaneous EEG-fMRI of decision making in juvenile attention deficit/hyperactivity disorder (ADHD)

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Attention deficit/hyperactivity disorder (ADHD) is with a frequency of 5-8 % one of the most prevalent psychiatric disorders and has been associated with decision making deficits. Moreover, there are many findings associating ADHD with impairments in the dopaminergic system. Models of ADHD have suggested that it may be caused by impaired reward prediction error (RPE) processing. RPEs reflect expectation violations and are known to be encoded by the dopaminergic midbrain. So far, however, only very little is known about the neural and behavioural correlates of RPE processing in ADHD. In this study, 40 adolescents (20 ADHD) played a probabilistic reversal learning task while simultaneous EEG-fMRI was recorded. To infer their decision making mechanisms, we fitted a Bayesian hierarchical Gaussian filter model (HGF) to the behaviour. We analyzed RPEs during cue and outcome presentation in the fMRI data. As an EEG-correlate of RPEs, we further analyzed and compared the feedback-related negativity (FRN). The modelling of the subjects' behaviour showed that ADHD patients had a less steep decision parameter, which means that they made more exploratory choices than the healthy controls. RPE processing in ADHD was impaired during cue as well as during feedback presentation in the medial prefrontal cortex (mPFC). Additionally, the FRN was impaired in ADHD. Furthermore, a single-trial source localization analysis of the FRN in the healthy controls revealed that this component is elicited by the same region as we found the RPEoutcome impairment. Using modelling and multimodal imaging, we were able to better understand the decision making deficits in adolescents with ADHD. We found that these impairments are

caused by more exploratory decision behaviour. Moreover, we found that these impairments are related to impaired RPE processing in the mPFC. Our findings give first insights into the impaired mechanisms of decision making and learning in ADHD.

## G9 Frontal cannabinoid system activation disrupts decision making based on different decision costs

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Endocannabinoids, principally fast retrograde signaling messengers, have emerged as fundamental modulators of synaptic function regulating a wide range of brain functions including feeding behavior, memory, stress responses, motor control and pain processing. The first cannabinoid receptor CB1 is highly abundant in many brain regions and has been implicated in many of these functions. Despite the evidence for altered decision making in cannabis abusers, the role of cannabinoid system in decision making circuits has not been studied. In the present study, our aim was to examine the role of cannabinoid modulation in cost-benefit decision making in the anterior cingulate cortex (ACC) and orbitofrontal cortex (OFC), key brain areas involved in decision making. Rats were trained to perform either a delay-based or an effort-based form of cost-benefit T-maze decision making task. On the test days, ACEA (a CB1 agonist), AM251 (a CB1 antagonist) or vehicle were locally administered either in the ACC in rats performing effort-based decision task or in the OFC in rats performing delay-based decision task. We have also performed Immunohistochemistry to determine co-localization of CB1 receptors on axonal ends of major neuronal populations in the areas. CB1 activation following ACEA administration resulted in a significant disruption of performance in both tasks while vehicle injection had no effect on the rats' performance. Control tasks with equal costs for large and small rewards ensured that the effects were specific for differential cost and benefit tasks and not general memory effects or spatial biases. Our results provide first direct evidence for the involvement of cannabinoid system in cost benefit decision making in the ACC and OFC.
We suggest that synaptic ends of both excitatory and inhibitory afferent neurons to these two frontal regions are modulated by cannabinoid signaling.

## G10 Developing Lexical Disambiguation: Semantic Networks and Executive Control in Children

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Aim: Lexical ambiguity is an inherent feature of many words and processing these words is tied up with the selection of one meaning while retaining the possibility that the alternative meaning must be selected. Proficient processing of ambiguous words such as homonyms thus requires a tightly structured semantic network and executive function skills such as inhibitory control and selective attention. Both of these components get developed in children with increasing linguistic experience and cortical maturation. A homonym test was designed to assess lexical ambiguity processing as a marker of such development in school- children; it might also be a tool in the assessment of deficient development.
Methods: The participants of this study were 3rd (n = 36) and 8th (n = 32) graders of Swiss public schools. Their ability to process lexical ambiguity was examined with a lexical decision task: sentences with an ambiguous word (homonym) priming the dominant or the non-dominant meaning and neutral sentences without an ambiguous word were followed by a target word related to the primed meaning or the non-primed meaning, a control word or a non-word. The stimuli were presented simultaneously in the visual and auditory modality; accuracy and reaction times were measured. Participants also performed a phonemic and semantic word fluency task to control for age-related skills in response inhibition and in maintaining and shifting attention. Fluency performance was measured in terms of clustering

and switching strategies.

Results: Accuracy rates and response latencies revealed a significant influence of age on ambiguity processing: 8th graders were found to make efficient use of context whereas 3rd graders showed a more lexically biased pattern of response, reflecting a semantic network in which the two meanings of a homonym are not yet tightly linked. This difference between the two age groups with respect to the processing of homonyms was supported by their differential performance in the semantic fluency task: 8th graders produced significantly more clusters and switches than 3rd graders. In the phonemic fluency task the mean number of clusters produced by the two age groups did not differ significantly.

Conclusion: The differential pattern of performance of the two age groups in the two tasks provides supportive evidence for the relationship between an age-related development of a structured lexical-semantic network and cortical maturation, in particular executive function skills.

## G11 Predicting benefits of multisensory memories

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Single encounters with multisensory auditory-visual pairings are sufficient to impact subsequent unisensory object recognition [Thelen et al., 2012]. Recognition accuracy for images that had been paired with a meaningless sound upon their initial encounter (V+) is generally impaired when compared with recognition accuracy of images encountered only visually (V-) during a continuous recognition task. This behavioral decrement correlates with differential neuronal activity at 270ms-310ms post- stimulus onset within middle temporal cortices. Moreover, activity within these areas appears to be linked to the episodic nature of the meaningless encounters and/or to behavioral outcome, rather than re-activation processes of initial encounter context as proposed by the 'redintegration' theory. In order to address this hypothesis directly, we divided subjects into groups according to whether recognition accuracy for images paired with a meaningless sound upon initial encounter (V+) was impaired (group1) or enhanced (group2) with respect to images encountered only visually (V-).

We computed sensitivity (d') and response bias (c') measures to investigate differences between groups in terms of perception and response strategy. Data were submitted to a 2x2 ANOVA with between-subject factor of group and within-subject factor of modality (V- and V+). A significant group x modality interaction for d' and post-hoc paired t-tests revealed a significant decrease of d' in group1 (mean ± s.e.m.: d'(V-)= 2.96 ± 0.28; d'(V+)= 2.27 ± 0.30; t=3.218; p=0.024). Analyses on relative criterion (c') revealed a significant group x modality interaction, and post-hoc paired t-tests revealed a significant effect for c' for group2 (mean±s.e.m.: c'(V-)= -0.23±0.03; c'(V+)= -0.18±0.03; t=-4.189; p=0.009). This pattern suggests the two groups use distinct strategies to perform the task, either relying on perception or adopting a lax response criterion. To examine the neural bases of these strategies, we analyzed event-related potentials (ERPs). In terms of initial multisensory presentations, we observed a significant group by condition interaction at 270-316ms post-stimulus for the GFP. Further, this group difference was also observed at the level of source estimations. A significant group by condition interaction within right temporal regions at 270- 346ms post-stimulus was observed, suggestive of differential underlying multisensory processing that may explain the opposing behavioral outcome during unisensory repetition discrimination.

## G12 The influence of positive and negative valence of events on the intention superiority effect over the life-course

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According to the intention superiority effect, people remember more future intentions than past events. Moreover, several studies have shown a facilitation of retrieving positive events. The aim of the present study was to investigate the influence of age on the intention superiority effect for both, positive and negative events. We asked a group of young and a group of older adults to report their remembered future intentions and past events from a specific time-window. Additionally, we prompted them to value each retrieved memory as positive or negative. We expected to find more positive than negative reported future intentions and past events in both age-groups. Critically, we hypothesized an intention superiority effect for positive memories
in the young adults group only, but no intention superiority effect in the older adults group. These results would suggest that the intention superiority effect is based on positive intentions and it decreases with constricted future time perspective in older adults.

## G13 Ecological Validity of Virtual-Reality-Daily-Living-Activities screening for early dementia: A longitudinal study

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Background: Dementia is a multifaceted disorder that impairs cognitive functions, such as memory, language, and executive functions necessary to plan, organize, and prioritize tasks required for goal-directed behaviors. In most cases, individuals with dementia experience difficulties interacting with physical and social environments. The purpose of this study was to establish ecological validity and initial construct validity of a fire evacuation Virtual Reality Day-Out Task (VR-DOT) environment based on performance profiles as a screening tool for early dementia.
Objective: The objectives were (1) to examine the relationships among the performances of 3 groups of participants in the VR-DOT and traditional neuropsychological tests employed to assess executive functions, and (2) to compare the performance of participants with mild Alzheimer's-type dementia (AD) to those with amnestic single-domain mild cognitive impairment (MCI) and healthy controls in the VR-DOT and traditional neuropsychological tests used to assess executive functions. We hypothesized that the 2 cognitively impaired groups would have distinct performance profiles and show significantly impaired independent functioning in ADL compared to the healthy controls.
Methods: The study population included 3 groups: 72 healthy control elderly participants, 65 amnestic MCI participants, and 68 mild AD participants. A natural user interface framework based on a fire evacuation VR-DOT environment was used for assessing physical and cognitive abilities of seniors over 3 years. VR-DOT focuses on the subtle errors and patterns in performing everyday activities and has the advantage of not depending on a subjective rating of an individual person. We further assessed functional capacity by both neuropsychological tests (including measures of attention, memory, working memory, executive functions, language, and

depression). We also evaluated performance in finger tapping, grip strength, stride length, gait speed, and chair stands separately and while performing VR-DOTs in order to correlate performance in these measures with VR-DOTs because performance while navigating a virtual environment is a valid and reliable indicator of cognitive decline in elderly persons.
Results: The mild AD group was more impaired than the amnestic MCI group, and both were more impaired than healthy controls. The novel VR-DOT functional index correlated strongly with standard cognitive and functional measurements, such as mini-mental state examination (MMSE; rho = 0.26, P=.01) and Bristol Activities of Daily Living (ADL) scale scores (rho = 0.32, P=.001).
Conclusions: Functional impairment is a defining characteristic of predementia and is partly dependent on the degree of cognitive impairment. The novel virtual reality measures of functional ability seem more sensitive to functional impairment than qualitative measures in predementia, thus accurately differentiating from healthy controls. We conclude that VR-DOT is an effective tool for discriminating predementia and mild AD from controls by detecting differences in terms of errors, omissions, and perseverations while measuring ADL functional ability.

## G14 Reduced Ultrasonic Vocalizations in Rats after a Kainic Acid-Induced Lesion of the PV1- Foxb1 Nucleus

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We are currently investigating the function of a newly detected nucleus (PV1-Foxb1, as neurons express either parvalbumin [PV] or Foxb1) in the ventrolateral tuberal hypothalamus of mice and rats. Based on its location within the medial forebrain bundle as well as on its projection into the ventrolateral periaqueductal grey, we hypothesize an involvement of the PV1-Foxb1 nucleus in the regulation of the expression of emotions (vocalizations), amongst others. To test this hypothesis, a group of adolescent Wistar rats was tickled as described before. It is well known that tickling is a positive reinforcer that can induce positive affect in socially isolated rats, which will thereupon emit ultrasonic vocalizations in a frequency range around 50 kHz (positive USV).
After weaning, twelve Wistar rat pups were housed individually during four weeks, in which each rat underwent twelve tickling sessions. After a baseline period consisting of the first two weeks, test animals (n=8) received a bilateral stereotactic injection of kainic acid into the region of the PV1-Foxb1 nucleus. Control animals received either a comparable injection of saline (n=2) or just a comparable cut and suture of the skin (n=2). During all tickling sessions, USV were recorded using specialized equipment. After perfusion, the number of PV-immunoreactive (PV-ir) cells that remained in the PV1-Foxb1 nucleus of every rat was estimated from fluorescence micrographs. Based on PV-ir cell numbers, test animals were classified as successful or mediocre lesions. In a group of 5 rats, clearly classified as successful lesions, the number of positive USV fell to almost zero during the first four tickling sessions after the treatments, whereas it remained relatively constant or even increased in the other groups (mediocre lesions, saline, suture). Overall, the total number of remaining PV-ir cells correlated with the treatment- associated change in the number of positive USV.
These results suggest a role of the lesioned structures in the expression of vocalizations. As axons of the medial forebrain bundle, passing through the PV1-Foxb1 nucleus, are not expected to express kainate receptors, the neurons making up the PV1-Foxb1 nucleus are more likely responsible for the effects induced by the lesions.

## G15 Effects of age and eccentricity on visual search performance

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The aim of this study was to examine the effects of aging and target eccentricity on a visual search task comprising 30 images of everyday life projected into a hemisphere, realizing a ± 90° visual field. The task performed binocularly allowed participants to freely move their eyes to scan images for an appearing target or distractor stimulus (presented at 10°; 30°, and 50° eccentricity). The distractor stimulus required no response, while the target stimulus required acknowledgment by pressing the response button. 117 healthy subjects (mean age=49.63 years, SD=17.40 years, age range 20-78 years) were studied. The results show that target detection performance decreases with age as well as with increasing eccentricity, especially for older subjects. Reaction time also increases with age and eccentricity, but in contrast to target detection, there is no interaction between age and eccentricity. Eye movement analysis showed that younger subjects exhibited a passive search strategy while older subjects exhibited an active search strategy probably as a compensation for their reduced peripheral detection performance.

## G16 Left temporal alpha-band activity reflects single word intelligibility

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Investigations of the electroencephalographic (EEG) correlates of degraded speech perception have often been inconclusive as to whether observed differences in brain responses between conditions result from different acoustic properties of more or less intelligible stimuli or whether they relate to cognitive processes implicated in comprehending challenging stimuli.

In this study we use noise vocoding to spectrally degrade monosyllabic words in order to manipulate their intelligibility. We used spectral rotation to generate incomprehensible control conditions matched in terms of spectral detail. We recorded EEG from 14 volunteers who listened to a series of noise vocoded (NV) and noise-vocoded spectrally-rotated (rNV) words, while they carried out a detection task. We specifically sought components of the EEG response that showed an interaction between spectral rotation and spectral degradation. This reflects aspects of the EEG response that are related to intelligibility of acoustically degraded monosyllabic words, while controlling for spectral detail.

Analyses of event-related potentials showed an interaction effect for a P300-like component at several centro-parietal electrodes. Time-frequency analysis of the EEG signal in the alpha-band revealed a monotonic increase in event-related desynchronization (ERD) for the NV but not the rNV stimuli in the alpha band at a left temporo-central electrode cluster from 420 -560ms reflecting a direct relationship between the strength of alpha-band ERD and intelligibility.

## G17 Sound recognition is influenced by single-trial multisensory memories

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Prior research has demonstrated that unisensory object recognition is affected by previous single-trial multisensory memories both within the visual and the auditory modality. Object recognition is improved for stimuli that have been previously encountered as paired with a semantically congruent stimulus in the task-irrelevant modality and impaired for stimuli that have been previously encountered as paired with a semantically incongruent or meaningless stimulus, when compared to stimuli that have been encountered alone. Only visual recognition has thus far been investigated with neuroimaging techniques. Differential brain responses were found during early processing stages (~100ms post-stimulus onset) between pictures that were initially paired with a sound and pictures that were presented alone. Enhanced recognition memory led to a modulation in lateral- occipital cortices while impaired recognition memory led to a modulation in middle-temporal cortices.
Here, a combined psychophysical and electrical neuroimaging study was conducted to investigate the influence of multisensory memories on later auditory object recognition. Results show that auditory object recognition is affected by prior multisensory experiences. Detection sensitivity was enhanced for sounds that had been previously paired with congruent images and for sounds that had been previously paired with meaningless images; both compared to sounds that were previously encountered alone. Analysis of ERPs showed that differences between conditions manifested between 240–262ms post-stimulus. Source estimations showed that these differences stemmed from modulation within occipital cortices. Post-hoc analyses showed that these areas were activated more strongly for sounds that were previously encountered alone when compared to sounds that were encountered with an image. These results indicate that visual cortex processes repeated sounds differently according to their initial encounter context.

## G18 Tracing neuronal circuits of fear using rabies-based tools

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The amygdala is essential for the acquisition, storage and retrieval of emotional memories, and is implicated in many psychiatric disorders. The amygdala output nuclei, especially the central nucleus (CeA), receive convergent information from several other amygdala regions and other brain regions and project to hypothalamic and brain stem nuclei to regulate the behavioural and physiological expression of fear. To elucidate the neural circuit mechanisms underlying fear memories, it is essential to understand how neural circuits in the CeA are connected with their upstream inputs and downstream targets that involved in distinct physiological functions and animal behaviours. However, it is still largely unknown and limited by the difficulties to image interconnected neuronal circuits and identified synaptic connections. To tackle this problem, we use rabies virus-mediated transsynaptic tracing to probe anatomic projection pathways which regulate distinct aspects of fear responses via CeA. The modified rabies virus that we use can only retrogradely trace presynaptic neurons connected by one synapse (monosynaptic tracing). We first applied this approach to CeA output neurons projecting to the periaqueductal gray (PAG), the nucleus of the solitary tract (NST) and the locus coeruleus (LC) which regulate freezing behavior, cardiovascular reactivity and arousal, respectively. The CeA output neurons are found in both lateral and medial subdivisions of CeA (CeL and CeM). Then, we enabled the rabies to transsynaptically trace the upstream presynaptic neurons of those CeA neurons by the complement of rabies glycoprotein in CeA output neurons. We observed extensive disynaptic labeling in caudate putamen (CPu) and posterior ventral hippocampus and moderate labeling in the lateral posterior part of the basal amygdala (BLP) and in the dorsal lateral part of the lateral amygdala (LAdl) where labeling was rarely seen by monosynaptic tracing. We also observed extensive labeling in CeC (capsular part of CeA)

and CeL where CeA output neurons are intermingled with their local upstream neurons. Next we performed simultaneous tracing with rabies-GFP and rabies-RFP injected in the PAG and NST of the same animal, respectively. Interestingly, we found that 60-80% cells in CPu and hippocampus form part of both projection pathways. Then, we selectively traced upstream neurons projecting to CeA neurons which target both PAG and NST. This experiment also revealed extensive labeling in CPu and hippocampus. Taken together, these results indicate that CeA output neurons, at least in part, project to multiple targets in the brain stem, and receive converging input from upstream brain structures such as the CPu and the hippocampus. We are currently combing transsynaptic tracing with optogenetic approaches to examine how these pathways regulate distinct aspects of fear behavior.

## G19 Gesture performance is associated with understanding of nonverbal social information and postural knowledge in patients with schizophrenia

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Background: We have recently demonstrated gestural deficits in schizophrenia using a standardized test (test of upper limb apraxia; TULIA). The errors made by schizophrenia patients were comparable to those made by patients with apraxia. Furthermore, the recognition of nonverbal social cues is impaired in schizophrenia, including gestures. In fact, nonverbal social perception (including the analysis of co-speech gestures) is a mediator of functional status in schizophrenia. We aimed to test whether gesture performance, gestural knowledge and the recognition of social cues were associated.

Methode: 13 patients meeting DSM-5 criteria for schizophrenia were investigated using comprehensive behavioral praxis tests for gesture performance (TULIA), gestural knowledge (postural knowledge task, PTK) and nonverbal social perception (profile of nonverbal sensitivity, PONS). The structured TULIA assessment was recorded on video and the video recordings of the participants were rated by an independent, blinded expert. Partial correlations were computed to test associations of gesture perception (TULIA) with gestural

Results: Schizophrenia patients are impaired in gesture production, recognition and nonverbal social perception. Poor nonverbal social perception is associated with impairments in gesture recognition ($r = 0.59$, $p = 0.020$) and performance ($r = - 0.49$, $p = 0.089$). Furthermore, poor gesture recognition is associated with impaired gesture performance ($r = 0.65$, $p = 0.016$).

Diskussion: Gesture performance and recognition as well as the understanding of social nonverbal information were interrelated in patients with schizophrenia. We have previously demonstrated an association of gesture performance with frontal lobe function and motor behavior in schizophrenia. The present preliminary results suggest that schizophrenia patients are impaired in gesture perception and performance and that patients who present with these deficits will also suffer from poor nonverbal perception. Therefore, the basic problem of poor gestural performance may contribute to impaired social cognition in schizophrenia.

## G20 Mouse models for the study of the stress-inflammation-dopamine hypothesis for depression

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Understanding the aetio-pathophysiology of depression is the route to identification of efficacious anti-depressant strategies. Animal models are essential in this process. A major theory is that stress-induced inflammation is aetiological in depression and that one of its effects is to alter dopamine and serotonin signaling leading to symptoms of negative mood, helplessness, anhedonia and fatigue. Mice exposed to a form of chronic psychosocial stress, chronic social defeat (CSD), exhibit decreased motivation for reward, increased learned helplessness and increased fatigability. These behavioural effects of CSD co-occur with peripheral immune-inflammatory activation including splenomegaly and increased serum titres of pro-inflammatory cytokines IL-6 and TNF-a. Genome-wide gene expression analysis revealed an increased expression of inflammation pathway genes in several brain regions of CSD mice, including the medial prefrontal cortex and the amygdala. In the amygdala, expression of genes involved in the dopamine pathway exhibited consistent changes in expression in CSD mice compared to CON mice: the dopamine receptors DRD2, ADORA2a and GPR88 were down-regulated and the monoamine transporter SCL29A4 was up-regulated. To investigate the role of dopamine in behaviours directed towards rewarding and aversive stimuli, including the changes in stimulus processing that underlie core symptoms of depression, dopamine depletion was achieved using the neurotoxin 6-hydroxydopamine (6-OHDA). Nucleus accumbens DA depletion led to decreased incentive motivation under high-effort conditions, increased learned helplessness and increased fatigability. These data support the stress-inflammation-dopamine hypothesis for depression and the mechanisms underlying changes in DA function will be studied to identify novel targets for restoring DA function as antidepressant treatment.

## G21 Does fear for pain affect disgust sensations? Cross-modal anticipatory effects between nociception and olfaction

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Studies on placebo effects and anticipation for pain showed that expectations can modulate our painful experience, with higher sensitivity when we are informed of the noxiousness of an upcoming event. However, it is still unknown whether these predictive representations code for the aversiveness or, more specifically, for the somatic content of the noxious event. We investigated this question by comparing two equally aversive, and yet somatically different, sensations: thermal pain and olfactory disgust. Through individual thresholding, we have selected two comparably unpleasant thermal and olfactory stimulations, which were presented following a pictorial cue. For each kind of stimulation (thermal, olfactory), four different cues were chosen informing about the occurrence of thermal-painful, thermal-painless, olfactory-disgusting and olfactory –non-disgusting events. This yielded to 8 balanced conditions, half of which were consistent (thermal cue followed by thermal stimulation), whereas the remaining half were inconsistent (thermal cue followed by olfactory stimulation). These trials intermingled with catch trials, in which extremely low or high unpleasant thermal/olfactory stimulations were preceded by consistent cues. Each trial was structured as follows: pictorial cue, stimulus delivery, and subjective rating of the stimulus. In line with the literature, we found a significant anticipation effect in consistent thermal trials (Atlas et al., 2010). Likewise we found a comparable anticipation effect for consistent olfactory trials. Critically, we also found significant anticipation effect when the cue was

inconsistent with the stimulation modality. These data suggest that the subjective experience of an event is modulated by the aversiveness of the preceding cue.

References:

1. L. Y. Atlas, N. Bolger, M. a Lindquist, T. D. Wager, Brain mediators of predictive cue effects on perceived pain., The Journal of neuroscience: the official journal of the Society for Neuroscience 30, 12964–77 (2010).

## G22 Observational Learning in Zebra Finches

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Observation can promote efficient motor and perceptual-discriminative learning in humans and animals. Humans performing arm reaching tasks under force field perturbations show significant increments in the rate of motor adaptation following a period of observing other participants performing an identical motion. Studies in primates and avian species have reported imitation learning of motor tasks involving dexterous movements such as opening lids from food jars (marmosets), or caps from milk bottles (Blue tits) .
We investigate whether Zebra Finches (Taeniopygia guttata) have the capacity for observational learning of a difficult auditory discrimination task. Briefly, pairs of adult male and female zebra finches are placed in adjacent cages in sound isolation chambers, with one bird acting as a 'Demonstrator' for the other, an 'Observer'. We use a Go/No-Go operant conditioning protocol, where the reinforcing agent associated with one of the two stimulus classes is a strong puff of air applied one second after stimulus offset (the air puff blows the bird off its perch). The perch is used as a vantage point by the Demonstrator to interact with the Observer. Demonstrators eventually learn to stay or leave the perch before the onset of the air-puff, providing the Observer with a behavioral response to the stimulus. After reaching a given performance criterion, we replace the Demonstrator with the Observer and subject it to the same task. We show that Observers need on average approximately a fourth of the number of trials required by Demonstrators to reach the performance criterion.

## G23 Dissecting cortical circuits dynamics underlying neuroprosthetic learning with a novel optical brain-machine interface

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Learning neuroprosthetic skills entails that a subject can volitionally control his own brain activity in a goal-directed manner. Such voluntary modulation of single or multiple neurons has been previously demonstrated in monkeys, humans and rodents using electrophysiological recordings. However, extra-cellular recordings only sample a small number of neurons and they suffer from limited means to longitudinally track the same neurons over time. In addition, they are agnostic to the identity and location of the recorded neurons within the cortex. Classical electrophysiology tools are therefore inadequate to study how local cortical circuits are reorganized during the learning process. We have developed a novel optical brain-machine interface for head-fixed mice based on ultrafast two-photon population imaging of neurons expressing genetically encoded calcium indicators. This approach allows us to follow the circuit dynamics of thousands of neurons simultaneously across many weeks. The interface consists of a high speed two photon imaging system, able to stream images to storage, while extracting the activity of selected neurons online. The extracted activity is then transformed into real-time sensory or optogenetic feedback signals used for conditioning. We have successfully trained mice to voluntarily activate single neurons by delivering liquid rewards whenever the activity (and/or the associated feedback signal) surpassed

an arbitrary threshold. Mice learned to progressively increase the activity of selected neurons either across or within individual experimental sessions. In addition to the conditioned neuron, the activity of hundreds of neighbouring non-conditioned neurons was tracked longitudinally throughout the learning process. Our preliminary analyses reveal that the learning-related changes are highly specific to the conditioned neurons in comparison to the more stable activity of the non-conditioned neurons. We also observed a progressive significant increase in correlated activity in roughly 10% of neurons during learning. Conditioning of functionally characterized neurons further allowed us to assess the stability of pre-existing motor and sensory maps during the learning of arbitrary novel associations with single cell resolution.

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## G24 Dissociating target from flanker processing in visual crowding by EEG frequency-tagging

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In visual crowding, neighboring elements deteriorate performance on a target. The neural mechanisms of crowding are largely unknown. We have recently shown that the N1 component of the EEG is suppressed during crowding. It is difficult to disentangle the processing of the target and the flankers because they are presented synchronously. Here, we used a frequency-tagging technique to analyze EEG responses separately for the flankers and target. Subjects discriminated the offset direction of a vernier that was slowly increasing in size either to the left or right. The vernier and the flankers were either green or red and flickered at two different frequencies. Flankers of the same color as the vernier (green-green or red-red) crowded more strongly than flankers of a different color (green-red or red-green) because the former, as we propose, grouped with the vernier. EEG responses to the vernier were suppressed during crowding (same color flankers) compared to uncrowding (different color flankers). EEG responses to the flankers were slightly larger when the flankers grouped with the target compared to when they ungrouped from the target. Hence, EEG frequency tagging dissociates target and flanker processing. Our results suggest that, in crowding, the target is suppressed when it groups with the flankers while flanker-related activity increases or stays constant.

## G25 Navigational planning

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Spatial navigation and planning is assumed to involve a cognitive map for evaluating trajectories towards a goal. How such a map is realized in neuronal terms, however, remains elusive. Here we describe a simple and noise- robust neuronal implementation of a path finding algorithm in complex en- vironments. We consider a neuronal map of the environment that supports a traveling wave spreading out from the goal location. At each position of the map, local phase differences between adjacent neurons indicate the short- est direction towards the goal. In contrast to diffusion or single-wave-front models, local phase differences build up in time at arbitrary distances from the goal, providing a minimal and robust directional information through- out the map. The time needed to reach the steady state represents an estimate of an animal's waiting time before it is heading off to the goal. Given typical waiting times we estimate the number of neurons involved in the cognitive map. The model offers a functional interpretation of the en- hanced coherence in hippocampal-cortical oscillations during navigational decision making and interprets hippocampal forward and backward replay as a readout and update, respectively, of the cognitive map.

## G26 Anxiety influences social dominance and acts through the mesolimbic system.

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Dominance hierarchies occur in many species but the determinants are poorly understood. In outbred adult male Wistar rats we investigate the role of trait anxiety in social hierarchy formation. Animals classified as high (HA), intermediate (IA) or low (LA) anxious on the elevated plus maze (EPM) were matched for body-weight and differing (HALA-pairs) or similar (IAIA-pairs) anxiety profiles. Animals were then pair-wise placed in a novel cage and the animals started to spontaneously form a social hierarchy. Social dominance was determined by summarizing the durations of offensive-type behaviors. HA-animals were more likely to end up being submissive. A causal role for anxiety in the establishment of social hierarchy was found by peripheral treatment with the anxiolytic benzodiazepine diazepam which enhanced dominance behavior for HA-animals. We could mimick the peripheral effects of diazepam by intra-ventral tegmental area (VTA) infusions. Therefore we presumed that peripheral diazepam affects local GABA-ergic neurotransmission in the VTA. Indeed, intra-VTA infusion of the GABAa agonist muscimol reduced anxiety and enhanced social dominance. In contrast, the intra-VTA infusion of Bicuculline (GABAa antagonist) caused a rapid increase in anxiety-like behavior and also reduced social dominance. In line with our findings, benzodiazepines are known to modulate local dopaminergic efferents through GABA-ergic interneurons and as such may affect dopamine levels in the nucleus accumbens (NAc). Accordingly, we found that intra-NAc treatments in turn affected the formation of a social hierarchy; dominance behavior was reduced with muscimol but enhanced using a D1-like agonist. In contrast, the infusion of a D1-like antagonist alone or the infusion of a specific D2-like agonist lacked behavioral effect for social dominance. Our results highlight the personality trait anxiety in the establishment of social hierarchies and emphasize mesolimbic dopaminergic/GABAergic neurotransmission as possible underlying mechanisms. Anxiolytic treatments acting on the mesolimbic dopamine system might help overcome a predisposition to low status in highly anxious individuals.

## G27 Notch1 activity in mitral cells is odor dependent and contributes to olfactory behavior

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It has been previously shown that Notch1 signaling plays an important role in synaptic plasticity, learning and memory functions both in Drosophila and rodents. In this paper, we report that this feature is not restricted to hippocampal networks but also interests the olfactory bulb (OB). Olfaction and odor discrimination in rodents are innate and essential for survival. Notch1 expression is enriched in mitral cells of the mouse OB. These principal neurons are responsive to specific input odorants and project directly to higher brain structures. Olfactory stimulation activates a subset of mitral cells, which show increase in Notch1 activity. Notch1cKOKln mice display altered c-fos expression and decreased aversion to propionic acid as compared to wildtype controls. Extracellular recordings in the mitral cells layer in Notch1cKOKln and wildtype mice show that Notch1 regulates the magnitude of the neuronal response to olfactory stimuli. This indicates, for the first time, that Notch1 is involved in olfactory processing and contributes to olfactory behavior.

## G28 A Novel Paradigm for Investigating Motion Adaptation

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Previous research has shown that motion imagery draws on the same neural circuits that are involved in perception of motion, thus leading to a motion aftereffect (Winawer, Huk, & Boroditsky, 2010). Imagined stimuli can induce a similar shift in subjects' psychometric functions as neural adaptation due to a perceived stimulus. However, these studies have been criticized on the grounds that they fail to exclude the possibility that the subjects might have guessed the experimental hypothesis, and behaved accordingly. We demonstrate a novel paradigm for investigating behavioural effects of motion adaptation, based on a model of motion discrimination (Jazayeri & Movshon, 2006), which is not susceptible to demand characteristics. Using a model-based approach allows us to make strong predictions about subjects' responses under several motion adaptation conditions. We provide behavioural evidence from a motion adaptation task, which shows that subjects' performance is in agreement with our experimental predictions. These results provide a better baseline with which to compare subjects' performance in an imagery task. Furthermore, we use Bayesian techniques and multi-level modeling to obtain group-level parameter estimates, rather than using the traditional two-step approach to data analysis.

## G29 Source memory of visual imagery: a hierarchical multinomial processing tree model

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The present study investigated, based on a study of Finke, Johnson, and Shyi (1988) how the ease of imagery influences the probability of source confusions of perceived and imagined completion of natural symmetric shapes. The stimuli consisted of, slightly adapted, binary pictures of natural objects, namely symmetric pictures of birds, butterflies, insects and leaves. When inspecting the behavioral data of the source monitoring experiment, we could show that confusion of the sources becomes more likely, when the imagery process was relatively easy. However, if the converging processes of the source monitoring process, item memory, source memory and guessing biases, are disentangled, the interpretation of this effect must be reconsidered. The data was modeled with a hierarchical multinomial processing tree model, based on the latent-trait approach of Klauer (2010). This hierarchical model was extended by linear regressions, predicting the model parameters for every stimulus with the stimuli's features, ease of imagery and discriminability. After the data analysis with this model, not the source memory decreases, but the bias to guess that an item has been perceived, increases for easily imagined stimuli. Yet, the discriminability of the items is influencing the item memory accuracy.

## G30 Optogenetic loss-of-function mapping of cortical motor circuits involved in voluntary action

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The motor cortex consists of several interconnected sub-regions playing roles in specific aspects of voluntary movements. A classical approach to attribute function to specific brain areas is local inactivation. However, most silencing techniques are irreversible, invasive or lack the behaviorally relevant time and spatial resolution. In order to overcome these limitations, we developed a non-invasive optogenetic approach to inactivate cortical activity in head- fixed mice. We trained mice to discriminate between two sensory stimuli and report their answer by moving a joystick to one of two positions. Correct answers given within two seconds after the stimulus

delivery were rewarded with water. We tracked forelimb movements and other motor output variables over hundreds of trials per session using automated behavioral control systems. To transiently silence specific motor areas, we used a high resolution optogenetic mapping method. The different motor areas in the ipsilateral, contralateral or both hemispheres were inactivated through the intact skull using a laser scanning system or miniature LEDs. Our results show that transient inactivation of the different cortical areas affects very selective aspects of the motor output. We found for example that contralateral motor cortex inactivation significantly delayed pushing movements, whereas pulling dynamics appeared only mildly affected. Motor cortex inactivation also increased the proportion of aborted trials. The effects of bilateral inactivation were in general stronger than unilateral inactivation alone. These preliminary results confirm the important role that motor cortex circuits play different aspects of in decision making, planning and execution of goal directed forelimb movements in mice.

This research is supported by the Swiss National Science Foundation and the Medical Faculty of the University of Geneva.

## G31 The brain's default state interacts with working memory processes in a complex and load- dependent manner

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Recently, many studies about a network active during rest and deactivated during tasks emerged in the literature: the default mode network (DMN). Spatial and temporal DMN features are important markers for psychiatric diseases. Another prominent indicator of cognitive functioning, yielding information about the mental condition in health and disease, is working memory (WM) processing. In EEG studies, frontal-midline theta power has been shown to increase with load during WM retention in healthy subjects. From these findings, the conclusion can be drawn that an increase in resting state DMN activity may go along with an increase in theta power in high-load WM conditions. We followed this hypothesis in a study on 17 healthy subjects performing a visual Sternberg WM task. The DMN was obtained by a BOLD-ICA approach and its dynamics represented by the percent-strength during pre-stimulus periods. DMN dynamics were temporally correlated with EEG theta spectral power from retention intervals. This so-called covariance mapping yielded the spatial distribution of the theta EEG fluctuations associated with the dynamics of the DMN. In line with previous findings, theta power was increased at frontal-midline electrodes in high- versus low-load conditions during early WM retention. However, load-dependent correlations of DMN with theta power resulted in primarily positive correlations in low-load conditions, while during high-load conditions negative correlations of DMN activity and theta power were observed at frontal-midline electrodes. This DMN-dependent load effect reached significance during later retention. Our results show a complex and load-dependent interaction of pre-stimulus DMN activity and theta power during retention, varying over the course of the retention period. Since both, WM performance and DMN activity, are markers of mental health, our results could be important for further investigations of psychiatric populations.

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## G32 Experience-dependent plasticity changes across human development

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One of the greatest challenges for our brain is to constantly adapt to an ever-changing environment, which it does largely through processes of experience-dependent synaptic plasticity. The developing brain is assumed to be highly sensitive to novel experiences, leading to a great capacity to learn and to memorize. However, empirical evidence for this is rather scarce. Local sleep slow wave activity (SWA, EEG power < 4.5Hz) can be used not only as a marker of synaptic changes in response to experiences; it is itself causally related to behavioural changes such as the improvement of skills. Here, we investigated in three different age-groups (children: 9-11 yrs, n=15; adolescents: 12-17 yrs, n=14; adults: 18-25 yrs, n=17) i) local changes in SWA after performing on a visuomotor adaptation task as a measure of synaptic plasticity, ii) overnight changes in visuomotor performance and iii) whether both measures are related. In children but not in the older age-groups, SWA was up-regulated after visuomotor adaptation in a region over the right parietal cortex that is known to be involved in this task. Moreover, we found significant overnight changes in visuomotor performance, which were fundamentally different in the three age-groups and correlated with local changes of SWA. Our data strongly support the idea that the capacity for experience-dependent plasticity decreases from childhood to adulthood and that the brain is most vulnerable to a specific learning experience at the time during which those cortical regions that are involved in this experience undergo maturation. Our behavioural data suggests profound age-dependent differences in the sleep-related modification of new experiences: during childhood the brain seems to preferentially stabilize well-established rather than newly acquired memory traces whereas at a later developmental stage new and old memory traces are equally strengthened during sleep.

## G33 The eye contact effect during an emotional working memory paradigm

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From birth the direct gaze may be early dissociated from averted gaze (Farroni et al. 2001). Several studies have shown specialized neural circuits involved in gaze processing (Itier, 2009), including the superior temporal sulcus, the amygdala, the fusiform gyrus, frontal and parietal areas. The functional connections between these areas are poorly understood but seem to vary as a function of emotional context and the cognitive processes involved. It has been shown that negative emotion facilitate working memory (WM) for face identity (Jackson et al. 2013). This high density EEG study examines the temporal dynamics of gaze direction perception, during a working memory (WM) task. With this aim, neutral faces with direct and averted gaze were presented in a 2-back WM paradigm. ERP results for 'not repeated faces' show that the perception of averted gaze relative to direct gaze evoked a stronger P100, suggesting a gaze effect at early stages. Furthermore, in both conditions WM load modulated the N170 and the P300 (amplitude decreased as WM load increased), with late changes in topographies. Behavioral results indicate that faces with averted gaze were recognized more accurately on the first presentation. Under WM load this initial advantage for averted gaze lead to better performance. Interestingly, subject ratings of emotional perception revealed a negative bias in emotional judgment for both conditions. Our results indicate that gaze perception has a strong effect on first presentation which seems to be also present after the second presentation.

## G34 Ultrarapidly presented visual stimuli affect processing of subsequent categorical information

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Masking visual stimuli has been the conventional approach to prevent a stimulus to become conscious during visual presentation. Using this approach it has been shown that subliminal primes can induce covert motor response detectable in both EEG and fMRI activity. That implies a cognitive level of processing for stimuli which do not enter consciousness. The mechanisms leading to this motor bias are still poorly understood.In the present study, we used a visual categorization task in combination with ultrarapid tachistoscopic presentation as an alternative to masking. Subjects were not aware of the presented visual primes. These primes preceded categorically identical or different targets to which the subjects had to respond, being either objects or faces. Using this novel stimulation approach, we showed that these preconscious primes were affecting the behavioral performance of the categorization task regarding response times. Furthermore, this behavioral slow-down during incoherent prime-target pairs was also mirrored in the EEG data acquired. Similarly to previous studies we alsoobserved covert motor responses induced by priming. More notably, we find priming-related traces arising as early as 70 ms post-target time. This implies that priming related effects start already at a lower-level, i.e. rather perceptual basis of these effects than the previously reported covert motor response effects. These results demonstrate the usefulness of tachistoscopic priming and open up new possibilities of experimental designs for induction of subliminal effects without the need for visual masking.

## G35 CRF Neurons in the Central Amygdala Mediate Conditioned Active Fear Behavior

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The selection of appropriate behavioral responses to potentially dangerous environmental stimuli is fundamental to the survival of organisms. The amygdala is critical for emotional learning and is a central mediator of important behavioral strategies, including conditioned active and passive fear responses. The central nucleus of the amygdala sends projections to numerous brain centers which may mediate the switch between active and passive fear behaviors; however, the significance and function of specific projections remains unclear. We have developed a unique conditioning paradigm in which two sets of auditory stimuli are presented in series, followed immediately by footshock. Following only one day of conditioning, mice develop an active response to the white noise component of the compound stimulus while maintaining a passive freezing response to the pure tone component. We recorded neuronal activity in the central lateral amygdala of behaving mice during the conditioned flight paradigm. We observed neurons which developed strong responses to white noise and shock. Interestingly, this neuronal activity was correlated with active defensive responses. To determine a candidate neuronal subpoulation within the central amygdala, we performed virus vector-based anterograde tracing experiments. Our results show that the CeA CRF network sends projections to several brain regions important for active fear responding. We then expressed the excitatory opsin ChR2 specifically in CRF neurons and used short latency responses to brief pulses of light to identify CRF neurons during awake, behaving single-unit recordings. Identified CRF neurons develop responses to both WN and shock, phases of the behavior in which there is a high degree of active behavior. Other groups of mice were injected with viruses conditionally expressing ChR2 or ARCH specifically in CRF neurons. Activity of CRF neurons was manipulated during WN in the conditioned flight paradigm. ARCH-mediated inhibition of CRF neurons during WN presentations completely blocked active defensive responses. Finally, a mutated rabies-based approach was used to determine the inputs to the CeA CRF network. A restricted set of inputs was observed, stemming from homeostatic and limbic regions. Taken together, these results suggest that CRF neurons of the central amygdala mediate conditioned active fear responding.

## G36 Hierarchical network of vocalizations in songbird groups

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Vocalizations are an essential part of social interactions in birds. They have important biological functions in coordinating activity of group members. However, little is known about the structure of vocal interactions in bird groups. The main challenge for investigating vocal interactions and their biological significance in a bird group is to discriminate individual vocalizations of rapidly moving, sometimes simultaneously vocalizing individuals. We make use of recently developed back-attached ultra- miniature sound/acceleration recorders (SfN 2011, 692.08) and recorded vocalizations in groups of freely moving laboratory- housed zebra finches. Conveniently, the microphone picked up sounds from several birds, whereas the accelerometer recorded vocalizations only produced by the carrier. Accelerometer signals consisted of high-quality audio recordings up to almost 5 kHz, well suited for perfect classification of vocal elements even in the midst of other birds vocalizing. We studied 3 groups of 4 male birds each and recorded their vocalizations during several days in a sound-proof chamber. We collected data during 2.5 morning hours when vocalization density was highest. Every other day during the 2.5 morning hours we introduced a female to the group to study the development of vocal interactions between the males and the female. We measured the strength of pairwise interactions between birds by computing cross-correlation (CC) functions of the number of selected vocal elements in sliding 250 ms time windows. To create a linear ranking of birds we also computed CC functions between calls in a given bird and calls in all other birds, to sort the birds by the times of their CC maxima (within a range of time lags typically smaller than 200 ms). This ranking reflects the average order of calls in the entire group. We have found that communication networks determined by CCs in zebra finch groups have a stable hierarchical structure. The networks form rapidly in newly created groups and strengthen over the course of several days, where the strengthening is manifested in faster and more reliable call-call responses. Singing behaviors differed between individuals. Some animals tended to sing together whereas others avoided that tendency. Introduction of the female strongly decreased the number of songs produced by males and changed the hierarchy of their call interactions within the entire group. However, after female removal the original hierarchy recovered in most cases. These findings of rapid hierarchy formation suggest the existence of strongly pairwise attractive rules for the formation of communication networks that depend on the group composition as a whole.

## G37 Developmental changes in the dopamine system link maternal infection to reward deficits and obesity

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Background: Obesity is associated with abnormal sensitivity to food reward and aberrations in the dopaminergic system, one of the main neurobiological substrates for reward-related functions; yet it is still unclear whether such abnormalities emerge as neuroadaptive responses to overeating or whether they represent vulnerability factors promoting the development of obesity. Using a mouse model of maternal immune challenge (MIA), the present study evaluated whether immune-mediated disruption of dopaminergic development can lead to reward deficits prior to the emergence of obesity.

Methods: Pregnant mice were injected with the viral mimetic poly(I:C) or vehicle in late pregnancy. Brains were harvested for immunohistochemistry from both peripubertal and adult offspring. Willingness to run for food reward and sucrose-conditioned place preference were assessed in adult animals. Finally, body weight was monitored in mice exposed to a palatable high fat diet.

Results: MIA led to increased striatal levels of dopamine receptor 2 (D2R) in peripuberty, but reduced levels in adulthood (accompanied by reduced D1R and dopamine transporter levels) (all $p<0.05$; $n=5$ per group per sex). MIA-offspring also displayed reduced motivation to run for food ($p<0.05$; $n=9$) and place-preference for sucrose ($p<0.05$; $n=18$), suggesting decreased sensitivity to food reward. Finally, MIA-

offspring demonstrated higher propensity to diet-induced obesity ($p<0.05$; n=9). Strikingly, these effects were almost exclusively restricted to the female sex, as revealed by significant sex x treatment interactions.

Conclusions: We here describe a novel neurodevelopmental mouse model in which aberrant dopaminergic function and reward deficits precede the development of obesity. Our findings suggest that early changes in the dopaminergic system could (sex-dependently) increase the vulnerability to obesity, though direct evidence for such hypothesis is still warranted.

## G38 Characterization of the sleep pattern and behaviour in dopamine neuron-specific orexin type 2 receptor knockout mice

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Orexins (OXs; Hypocretins), known as brain neuropeptides, are involved in energy metabolism and arousal levels regulation. OXs are produced in the hypothalamus that project throughout the entire brain, typically the main wake-promoting neuronal groups: noradrenergic (NA), dopaminergic (DA), histaminergic (HA), serotonergic (5-HT), and cholinergic (Ach) neurons. To dissect the orexin signaling in neuronal networks, we have created conditional knockout (CKO) alleles of each of the two Orexin-receptor gene and generated mice in which selective OX target neuron populations are depleted of either one or both receptors. Because OX neurons massively innervate the NA and DA systems that are intimately involved in narcolepsy symptoms, we generated NA and DA neuron-specific OX1R and OX2R deficient mice by crossing our mice to dopamine-beta- hydroxylase-driving Cre and dopamine transporter-driving Cre mice. We found loss of OX2R in dopamine neurons appears to affect the spectral quality of wakefulness, featuring notably higher EEG power density in theta oscillations. PS rebound after sleep deprivation appears decreased or delayed.

## G39 Environmental enrichment including exercise reverts high-altitude induced impairment of spatial and visual memory in rats

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Acute hypoxia, e.g. during a rapid ascent to high altitude (over 2500 m), is associated with memory impairment. One of the principal adaptive responses to hypoxia in the brain is VEGF induced angiogenesis. We have previously reported, that environmental enrichment (EE) can increase VEGF production and angiogenesis in the brain. It is currently unknown whether high-altitude induced memory impairment can be reverted by EE and exercise and if the vascular system interplay with cognitive functions. We investigated on the effect of EE and exercise in spatial and visual memory in Long Evans rats exposed to sub-acute high- altitude (3450m, Jungfrau Joch High Altitude Station, CH). Furthermore we investigated whether VEGF is involved in EE improved memory. Rats aged P40 were assigned to four different groups (n=8): rats raised in standard conditions (SC) and housed in SC at high-altitude (SC-SC); rats raised in EE and housed in SC at high-altitude (EE-SC); rats raised in SC and housed at EE at high-altitude (SC-EE) and rats raised at SC and orally treated with VEGF inhibitor (Vandetanib) during housing in EE at high-altitude (SC-EEinhib). At P49 animals were transported from 400 m (Zürich) to high altitude (3450m, Jungfrau Joch High Altitude Station, CH). Spatial memory was tested via the Object Displacement Test (ODT) and visual memory was tested via the Object Replacement Test (ORT). SC rats displayed a diminished memory performance with no differences in exploratory behavior. SC-EE rats improved significantly spatial and visual memory performance. This effect is mediated by VEGF, as SC-EEinhib rats showed cognitive features similar to SC-SC rats. Moreover the EE-SC rats showed an increased visual memory as compared to SC-SC rats, however, spacial memory was similar in both groups. Overall, EE and exercise can improve spatial and visual

memory in high-altitude. This effect is, at least in part, mediated by VEGF. Additionally, EE including exercise, before ascending to high altitude, improves visual memory. To confirm that memory impairment under SC and EE mediated recovery occurs only in rats exposed to high altitude, further experiments in Zürich will be realized. * We acknowledge the International Foundation High Altitude Research Station Jungfraujoch and Gornergrat (HFSJG), 3012 Bern, Switzerland, that made it possible for us to carry out our experiment(s) at the High Altitude Research Station at Jungfraujoch.

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## G40 Electrophysiological correlates of delinquent behavior in adults with ADHD symptomatology

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Background/aims: Attention deficit/hyperactivity disorder (ADHD) shows an increased prevalence in delinquents, thus being considered as a major risk factor for criminal behaviour. We investigated whether further neurophysiological abnormalities – besides ADHD - may promote delinquency in the presence of ADHD symptomatology.

Methods: We compared event related potentials (ERPs) of delinquent and non-delinquent subjects with ADHD symptoms and controls in a modified continuous performance task (VCPT) and a newly developed version of the task requiring emotional evaluation regarding topographies and Global Field Power (GFP), and compared the resting state EEGs (power spectra and topography).

Results: Delinquents with ADHD differed from non-delinquents with ADHD in the N170 and P200 (higher-order visual processing of objects and faces and facial affect), and in the LPC (late monitoring and evaluative functions of behavioural response inhibition. In the P300 Go (allocation of neural resources/cognitive processing capability), P300 Nogo (response inhibition), CNV (attention/expectancy), deviances were observed in both ADHD groups. Delinquents with ADHD symptomatology showed more beta power at frontal, central and parietal brain regions than non-delinquents with ADHD symptoms.

Conclusion: Our results suggest additional risk factors - besides ADHD symptoms - for delinquent behaviour in adults with ADHD symptomatology, consisting of deviant higher-order visual processing, especially of facial affect, abnormalities in monitoring and evaluative functions of response inhibition, and excessive beta power. The awareness of such risk-factors may be helpful in the assessment of the risk for delinquent behavior in a psychiatric context and may provide a neurobiological background for therapeutic interventions.

## G41 Neural effect of memory training in children born very preterm

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Background

There is mixed evidence regarding neural change following cognitive training. Brain activation increase, decrease, or a

combination of both may occur, possibly depending on the trained function or the type of training. The present study investigates training-induced neural change following two different types of memory trainings.

Methods

Very preterm born children (aged 7-12 years) were randomly allocated to a memory strategy training, an intensive working memory practice or a control group. Before and immediately after the training, cognitive performance was assessed and brain activation during a visual working memory task was measured using functional magnetic resonance imaging.

Results

Following both memory trainings, there was a significant decrease of fronto-parietal brain activation and a significant increase of memory performance. The magnitude of neural change in parietal brain areas correlated positively with the magnitude of change in working memory performance after the memory strategy training. In the control group, no neural or performance change occurred through the trainings.

Conclusion

These pilot data point towards a training-related decrease of brain activation, independent of the type of training. We provide evidence for neural and performance change following short memory trainings in very preterm born children which highlights the high functional plasticity of the child's brain during development.

## G42 Off-line consolidation in implicit sequence learning

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The main goal of this study was to investigate the contributions of general motor skill learning and sequence-specific memory consolidation in implicit sequence learning. Off-line consolidation was investigated in a serial reaction time task after intervals of 24 hours (Experiment 1) and 1 week (Experiment 2). In addition, we manipulated sequence complexity (deterministic vs. probabilistic) and whether responses were given uni- or bimanually. Evidence of off-line consolidation of general motor skill learning was found in both experiments and independent of kind of sequence and response type. In contrast, we did not find any evidence of off-line improvement in sequence-specific learning. These results suggest that sequence-specific consolidation needs online processing and active practice. Passive off-line learning seems to be specific to motor skill learning.

## G43 Influencing implicit task sequencing learning and consolidation with transcranial electric stimulation

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In implicit sequence learning participants learn a sequence of regularities without awareness. Typically, a serial reaction time task is used to investigate implicit learning. This task involves motor sequence learning. In contrast in the task sequence learning (TSL) paradigm, no motor sequence is involved and higher cognitive functions are necessary to extract the repeating sequence information. The purpose of this project is to investigate the role of the fronto-striatal system for implicit sequence learning and consolidation using transcranial electric stimulation. The participants will perform the TSL in two sessions. In the first session, they will receive transcranial electric stimulation directed to cortical areas that belong to fronto-striatal loops, that is the left or right dorso-lateral prefrontal cortex (DLPFC) or to the primary motor cortex (M1). Depending on the stimulated region we expect to enhance or inhibit implicit sequence learning. To evaluate

consolidation the TSL will be repeated in a second session. We expect that particularly the stimulation of the right DLPFC will boost sequence learning and the following consolidation.

## H. System Neuroscience and Neuroinformatics

### H1 The local circuit of cortical area Frontal Eye Fields in macaque cortex.

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In order to understand how cortex functions we need detailed knowledge of its structure. The usefulness of quantification in this approach is exemplified by the comprehensive connection matrix achieved for the cat primary visual cortex (Binzegger et al., 2004, Douglas et al., 1989). We now extend this approach to the macaque monkey cortex. Electron microscopy (EM) was used to examine cortex taken post mortem from two macaque monkeys used in other experiments licensed by the Kantonal Veterinaeramt, Zurich. We used the unbiased physical disector with modifications for rare events (Da Costa, 2009). Tissue was taken from frontal eye fields (FEF), area 8A, in one case from the exposed upper surface of the cortex and in the other case from the fundus of the sulcus. We find density ranges from 0.91 synapses per cubic micrometer in layers 1 and 4, to 0.6 in layers 5/6. Combined data from both animals gives a value of 0.83 synapses/mm3. About 7% of the synapses counted in the neuropil in both samples were symmetric, presumed inhibitory. Using physical disectors to estimate the density of nucleoli (and hence neurons) in toluidine blue stained material (Anderson et al., 2013) we find there are approximately 34300 neurons per cubic millimetre of cortex and therefore 24000 synapses per neuron in layer 3 of FEF. There are indications that FEF pyramidal cells have large cell bodies and bear more dendritic arborization than do the neurons of macaque areas V1 and 10. The relatively low cell densities in FEF are balanced by the higher number of synapses formed with each neuron consistent with the hub-like properties of FEF.

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### H2 The coaxial PV1-Foxb1-nucleus sends projections to the PAG

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The PV1-nucleus is a cord-like structure comprised of parvalbumin-positive neurons lodged within the ventrolateral hypothalamus. Indipendently, a stream of Foxb1-expressing neurons migrating to the ventrolateral hypothalamus was also described. We have found that parvalbumin-positive and Foxb1-expressing neurons intermingle together in the PV1-nucleus which, on the base of this discovery, has recently been redesigned as the PV1-Foxb1-nucleus. We mapped the efferent connections of PV1-Foxb1-nucleus using Cre-dependent viral constructs stereotactically injected in Foxb1-Cre and parvalbumin/Foxb1-Cre mice. The PV1-Foxb1-nucleus projects in two different directions, to a lesser extent in the prefrontal cortex rostrally, and in the periaqueductal grey (PAG) and hindbrain, caudally. The main projections sprout in two different bundles and reach the dorsolateral and the ventrolateral portion of the PAG. The connections between the lateral hypothalamic area and the PAG could be involved in several activities as modulating pain circuits and paves the way for further investigation to highlight important, yet undiscovered functions of the PV1-Foxb1-nucleus.

## H3 Infrequent simple cells in the tree shrew primary visual cortex

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There is a notable difference in the occurrence of primary visual cortex (V1) „simple“ and „complex“ cells between mammalian species, for example between cat and monkey. Here we are interested in examining occurrence of these two response types in the tree shrew, a close relative of primates. Two criteria are commonly used to separate the two cell classes: spatial separation of antagonistic receptive subfields responding to luminance in- and decreases (subfield overlap) and the temporal modulation by a drifting grating stimulus (F1/F0 ratio). Here we quantified both subfield overlap as well as F1/F0 ratio in 120 single neurons recorded from V1 of 16 anesthetized tree shrews. The proportion of “simple” cells found with the two different methods differed dramatically: Using the F1/F0 criterion approximately 42% of neurons were classified as “simple”, whereas using subfield overlap only 7% fell into this category. We argue that this discrepancy is in part explainable by the robust black dominance of a large majority of tree shrew V1 neurons which inflates F1/F0 modulation measures. In a subset of 72 neurons we repeated the measurements after stimulation of the basal forebrain (BF stim), the main source of cholinergic projections to cortex. BF stim led to robust increases in firing rates and significantly reduced F1/F0 ratios ($p<0.01$), such that 19 cells that were classified as “simple” before were now behaving like “complex” cells. Interestingly, the overlap indices were not systematically affected by basal forebrain stimulation ($p>0.1$). Taken together we show that in tree shrew V1, “simple” cells occur rather infrequently and structural receptive field measures like the subfield overlap appear to be more robust to changes in firing rate than the F1/F0 ratio. Our findings suggest that tree shrew V1 does not rely heavily on “simple” cell signals, and these may thus not represent an obligatory step in the transformation of visual information.

## H4 Cortical circuits matching body metabolic signals and behavior

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Signals from peripheral organs are known to influence mental processes. Neuroimaging studies have confirmed that cortical areas respond to changes in body physiological conditions and that these fluctuations affect psychology and behavior. Despite their important clinical implications, the pathways underlying these effects have been little explored. We investigated the role of insular cortex (IC) as an interface between interoceptive sensing and cognitive and emotional responses. In vivo glucoprivation by an i.p. administration of 2-deoxyglucose (2DG) increased anxiety-like behaviors and decreased risk avoidance in mice. This metabolic challenge also induced c-fos expression in a subpopulation of cells in IC, suggesting a putative link between IC metabolic-responsive neurons and behavior. To investigate the underlying cellular mechanisms we performed experiments on acute cortical slices. In vitro glucoprivation reproduced the patterns of c-fos expression observed in vivo, indicating that glucose sensing might occur locally. Whole-cell electrophysiological recordings further evidenced a set of neurons located in deep IC layers that respond to glucose in a cell-autonomous fashion, with either a glucose-inhibited or a glucose-excited phenotype. We are now looking at the identity of these neurons and characterizing the biophysical and molecular components of their responses to glucose changes.

## H5 Short-term facilitation as a normative consequence of presynaptic spike-rate adaptation

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Synapses are highly dynamical elements. On the hundreds of milliseconds time scale, their strength can increase (facilitate) or decrease (depress). Despite the ubiquity of this form of plasticity, called short- term plasticity (STP), the functional advantages of such a history-dependent synaptic strength remain elusive. Recently, it has been shown that short-term plasticity acts as the optimal estimator of the presynaptic membrane potential based on the observed past spike timings. A limitation of this model is the absence of an explicit mechanism for refractoriness of the presynaptic neuron. Here we expand the model by including refractoriness and adaptation effects and we show that this modification critically impacts the predictions on short-term plasticity. More specifically we show that in the presence of strong refractoriness the model predicts facilitation whereas short- term depression is predicted for neurons with weak refractoriness or even bursting properties. Those predictions can be proven analytically and are illustrated with numerical simulations. Finally, this new prediction on the link between refractoriness of the presynaptic neuron and facilitation of the downstream synapse is directly testable.

## H6 Membrane potential dynamics of stimulus-specific adaptation in mouse auditory cortex

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Neurons in sensory areas of the mammalian neocortex encode physical aspects of stimuli but are also influenced by contextual information. How physical and contextual stimulus aspects interact in cortical circuits comprising different cell types remains poorly understood. To address this question, we performed targeted in vivo whole-cell recordings from principal cells and interneurons in the primary auditory cortex of anesthetized mice. By characterizing membrane dynamics to pure tones of different frequencies and sound pressure level, we found clear evidence for frequency tuning in all three cell classes. On the other hand, interneurons were less well and more broadly tuned to sound frequency. In an oddball paradigm, we examined how stimulus context influences neuronal responses at different frequencies. Rare tones globally increased activity and sharpened tone discrimination in a cell type and stimulus-specific manner. These results elucidate how physical and contextual stimulus characteristics interact in heterogeneous cortical circuits and suggest a refined view of the microcircuit underlying processing of novel tones.

## H7 Right dorsal and ventral auditory pathways for processing vocal emotions

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Auditory processing of spoken language predominantly involves left ventral and dorsal pathways connecting temporal and frontal brain

regions for semantic and syntactic processing, respectively. Many recent studies provided a detailed description of these left ventral and dorsal pathways both for language processing, but also for sound processing in general. It is widely assumed that the right hemisphere similarly incorporates a ventral and dorsal pathway based on a proposed anatomical symmetry between the left and the right brain in terms of white matter anatomy. Only a few studies yet tried to determine the right auditory processing pathways between temporal and frontal cortices by combining functional and structural brain data. However, these studies provide only evidence for a possible dorsal pathway for speech prosody processing. In the present study we determined temporo-frontal connection pathways for the processing of emotional speech prosody between several subregions in superior temporal cortex (STC) and inferior frontal gyrus (IFG) using diffusion tensor tractography. Our results revealed two relevant findings: first and most importantly, we found both a dorsal and ventral pathway connecting temporal and frontal cortices with the strongest connection between a posterior region in right superior temporal sulcus (STS) and the right frontal operculum (FOP) and the right IFG. Second, whereas all temporal regions demonstrated a dorsal pathway to frontal regions, only the posterior STS and a region in the polare plane (PP) demonstrated a ventral pathway to frontal cortex. Finally, the connection probability between temporal and frontal regions was generally stronger for the dorsal compared with the ventral pathways. These findings have three important implications: first, the results show that also the right hemisphere incorporates dorsal and ventral pathways, which seem specialized for speech prosody processing. Second, compared to the left hemisphere, the right hemisphere however demonstrates a predominance of the dorsal compared with the ventral pathway indicating increased processing of dynamic temporal sound features (e.g. pitch contour), probably at lower time scales than the left hemisphere. Third, sensory-integrative regions in anterior STC showed connectivity mainly to FOP probably representing a pathway for processing invariant sound representations of speech prosody.

## H8 Temporal organization of EEG microstate sequences alters during pharmacologically induced loss of consciousness

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Using simultaneous EEG/fMRI, we have previously shown that the organization of EEG microstate sequences show long-range dependency and are monofractal over 6 dyadic scales covering the range from 256 ms to 16 s, which we postulated to be a necessary prerequisite for consciousness. In the present study, we assessed EEG microstate dynamics of the gradual loss of consciousness during induction of general anesthesia with the anesthetic propofol. In 6 healthy, awake, adult subjects, scheduled to undergo elective surgery requiring general anesthesia, 5 min of resting EEG (64 channels, acticap, BrainProducts) were recorded as a baseline. Propofol was then administered intravenously using a Target Controlled Infusion system and the pharmacokinetic model by Schnider et al. The initial effect-site (cerebral) concentration was 0.5 µg ml-1. Effect site concentrations were then increased stepwise by 1 µg ml-1 until 2.5 µg ml-1 and then by 0.5 µg ml-1 until loss of consciousness. After each increase, and once equilibration of the blood-brain concentration was reached, 5 min of resting EEG were recorded. Throughout the induction procedure, clinical assessment of patient consciousness was performed every minute using the Observer Assessment of Alertness/Sedation Scale (OAA/S). Long-range dependency of EEG microstate sequences decreased significantly both as a function of clinical assessment of consciousness (OAA/S) and propofol concentration. Our results suggest that this feature might indeed reflect an objective measure of pharmacologically induced loss of consciousness.

## H9 A computational model of auditory cortex to explore the role of GABAergic inhibition in age-related hearing loss

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Background
In adult mammalian cerebral cortex, most neurons can be classified as either excitatory principal cells (about 80%) or inhibitory interneurons (>10%). The cortical inhibitory neurotransmitter is gamma-aminobutryric acid (GABA), and post-mortem immunohistochemical studies have shown a reduction in the markers for GABAergic neurons in senescent primary auditory cortex. In separate studies, cortical electrophysiologal and behavioural responses to sound have been shown to differ between young and older subjects. Although these age-related differences have been assumed to be the functional outcome of GABAergic decline with age, it has not been shown how and whether GABA changes contribute to age-related hearing deficits. In order to explore this, a computational neuronal model is presented.
Method
Primary auditory cortex is modelled using a classic feed-forward network: excitatory thalamic neurons project onto excitatory principal (E) and inhibitory (I) cortical neurons. The architecture of cortico-cortical connections is based on published data from rat auditory cortical slices, and neurons are modelled as integrate-and-fire nodes using standard techniques. Excitatory and inhibitory synaptic currents are modelled as fast-acting, ionotropic currents. There are two free parameters to the model: 1) the pattern of current input to the thalamus, to model different acoustic stimuli and the quality of subcortical input which may deteriorate with age, and 2) the relative weight of GABAergic connections, to model the putative effects of cortical ageing. The model can be fit to either electrophysiological data, by considering the firing rate over time of a single E neuron, or behavioural data by using a signal-detection measure of the accuracy of acoustic discrimination based on the average firing rate across the population of E neurons.
Relevance
In contrast to in vivo studies where that both subcortical and cortical regions age, the current in silico model can be used to test whether age-related changes in cortical GABAergic activity exacerbate, compensate for, or simply reflect impoverished input to the cortex. To our knowledge no study has measured cortical GABA activity as well as electrophysiology or behaviour in the same subjects. The current model will be useful for interpreting the results of such experiments and for guiding future therapeutic approaches to the cortical component of age-related hearing loss.

## H10 Large scale imaging of neuronal structure in the mouse neocortex in vivo

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Sensory afferents in the granule cell layer of primary sensory cortical areas produce less than 15% of the synapses. Thus, the majority of cortical synaptic input originates from cortico-cortical circuits, mostly from local microcircuits, and not from the periphery. Yet, sensory stimulus can strongly influence perception and behavior. Accordingly, recent estimates of the number of cortical neurons required for perceptual decision tasks turned out to be much lower than previously assumed. We are developing methods to assess structural dynamics of small populations of cortical neurons whose activity is related to the learning of a perceptual decision task. We hypothesize that structural changes of the neurons that become engaged in the task will favour the downstream signaling needed for the behavioural performance. Dendrites and axons that come in close enough proximity of one another potentially connect. From a theoretical

perspective, the pattern and extent by which cortical neurons project their dendrites and axons maximizes the potential connectivity for a given length of wire. Hence, cortical microcircuits harbor a large repertoire of potential connectivity states, of which only one state is represented by the actual wiring diagram. As a result, the neural microcircuits could, in principle, perform new computations and acquire new functions by small changes in their synaptic wiring, such as by protruding dendritic spines and axonal boutons. We are interested in the structural mechanisms and strategies that cortical neurons use to change circuit function while learning a perceptual decision task. To investigate the relation between perceptual learning and neural structural dynamics, we record both phenomena in parallel over time. We have developed methods to rapidly and repeatedly image large volumes of supra-granular layers in the mouse cortex over months, using 2-photon laser scanning microscopy (2PLSM). We are developing a behavioral paradigm that engages the neuronal population that we assigned for 2PLSM.

### H11 A computational model of auditory cortex to explore the role of GABAergic inhibition in age-related

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In the olfactory bulb (OB) of zebrafish, odors evoke distributed patterns of activity across glomeruli that are reorganized by networks of neurons in deeper layers. This reorganization results in multiple computations including an equalization and decorrelation of activity patterns across the output neurons, the mitral cells. To understand the mechanisms underlying these computations it is essential to analyze the relationship between connectivity and odor specificity of OB neurons. We address this issue by first measuring odor-evoked activity patterns in vivo by multiphoton calcium imaging in larvae (4dpf). Subsequently, stacks of electron microscopy (EM) images from the same specimen are obtained by microtome-based serial block face scanning electron microscopy (SBEM). Using this approach, we have acquired complete EM stacks of larval OBs with a lateral resolution of 9-11nm per pixel and a section thickness of 20-30nm. The staining procedures used allow for the visualization of neuronal morphology and intracellular organelles including synapses. Skeletons of >1000 neurons in two OBs have been manually reconstructed by cohorts of trained humans. An analysis of proximity produced a putative connectivity matrix that will be refined into a synaptic connectome after synapse detection is complete. Preliminary analyses strongly suggest that the putative connectivity between subsets of neurons is non-random. In addition, the putative connectome revealed a possible new and rare interneuron type with hub-neuron like connectivity. In a semi-automated iterative alignment procedure we registered somata whose odor responses have been recorded by multiphoton calcium imaging to corresponding somata in the EM stack. This approach is being used to investigate whether the connectivity of OB neurons is related to their odor specificity. The exhaustive reconstruction of activity patterns and wiring diagrams in the same specimens is expected to provide novel insights into the topological organization of neuronal circuits and its relationship to circuit function. This information is fundamentally important to understand the mechanistic basis of neuronal computations.

## I. Brain Imaging

### I1 Will you feel it? The influence of brain states on conscious tactile perception.

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The role of fluctuating brain states, represented in EEG and MEG data by oscillatory activity, on upcoming processing of stimuli has attracted a lot of interest recently. In particular, pre-stimulus alpha band power (oscillations around 10Hz), modulated spontaneously or as a result of a task, has been shown to represent functional inhibition. Accordingly, the gating-by-inhibition hypothesis (Jensen and

Mazaheri, 2010) proposes that alpha power increases 'gate' information flow by inhibiting irrelevant brain areas. It is, however, unclear a) if this can be generalized to, e.g., the somatosensory modality and b) to what extend changes of functional connectivity are involved in the perceptual outcome and thus, in defining the brain states. In the present MEG study, we investigated the brain state beneficial for conscious perception in the somatosensory domain. We hypothesized that conscious tactile perception is preceded a) by decreased alpha band power in the somatosensory cortex, and b) by better functional connectivity between the somatosensory cortex and higher-order areas. Participants were asked to perform a tactile detection paradigm with stimulation at their perceptual threshold. As hypothesized, we found a relative alpha band power decrease in the somatosensory, premotor and superior temporal gyrus contralateral to stimulation prior to conscious perception. Furthermore, specific changes in functional connectivity patterns (based on graph theoretical measures) were associated with tactile stimulus detection. Our results provide further evidence that the influence of pre-stimulus alpha power on conscious perception is a general mechanism also found in the somatosensory domain. In addition, we show that not only oscillatory power changes define brain states beneficial for conscious perception but also functional connectivity patterns.

## I2 Repeatability of global and local network metrics in a test-retest of brain structural networks.

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Purpose: Whole-brain network analysis of diffusion imaging tractography data is an important new tool for quantification of structural connectivity patterns across individuals and between groups. In our study, data of 19 healthy subjects are used to analyze repeatability of global and local network metrics.

Methods: Each subject underwent two consecutives diffusion tensor imaging sequences. In addition, T1-weighted anatomical images were acquired to obtain a cortical parcellation and define the nodes of the network. Each region (ROI) of the parcellation was used as seed region for probabilistic tractography and an edge between two nodes existed if a nonzero connectivity index was found between the correspondent ROIs. The edge weight was defined as the proportion of streamlines connecting the two nodes corrected by the volume of the nodes [1]. The repeatability of the networks and the associated global and local metrics [2] were quantified by three different indices: the similarity of raw connection matrices, the intraclass correlation coefficient (ICC) and the coefficient of variation (CV) [3]. In addition, the effect of specific methodological characteristics on the metrics values and their repeatability was studied.

Results: Results showed good to excellent repeatability for global metrics (over all global metrics ICC: 0.8±0.1, CV: 3.4±2.9%), while for local metrics it was more variable and some metrics were found to have locally poor repeatability (ICC<0.5 or CV>15%). Our additional analysis suggests that it will be beneficial to have nodes of similar size.

Discussion: At the global level, our findings confirm previous results on the validity of global network metrics as clinical biomarkers for longitudinal measurements in healthy subjects ([3], [4]). However, the new results in our work indicate that the remaining variability at the local level as well as the effect of methodological characteristics on the network topology should be considered in the analysis of brain structural networks and especially in networks comparisons.

References: [1] Iturria-Medina Y. et al., NeuroImage, 2007 [2] Rubinov M. and Sporns O. NeuroImage, 2010 [3] Bassett D. et al. NeuroImage, 2011 [4] Owen J. et al. Brain Connect, 2013

## I3 Sensitivity of communicability metrics in the case of lesions in the brain structural network.

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Purpose: Computational network analysis offers new tools to quantify and analyze connectivity in brain structural networks. In our analysis, changes in the topology of brain structural networks in the case of simulated lesions are characterized by the use of several network metrics [2]. In particular, communicability related metrics have been included in the analysis ([3],[4]), as they account for indirect paths that may become more important in case of lesions.

Methods: Nineteen healthy subjects underwent two consecutives diffusion tensor imaging sequences. In addition, T1-weighted images were acquired to obtain a cortical parcellation and define the nodes of the network. Each region (ROI) of the parcellation was used as seed region for probabilistic tractography and an edge between two nodes existed if a nonzero connectivity index was found between the correspondent ROIs. The edge weight was defined as the proportion of streamlines connecting the two nodes corrected by their volume [1]. For each of the subjects, one network was used as baseline, while the other was damaged by simulated lesions. Lesions are simulated by partially or completely removing a node or an edge. The aims of the analysis were the comparison of the different metrics to detect nodes sensitive to lesions and the evaluation of local changes in the network metrics in the case of lesions.

Results: Measures of strength and communicability were the best to select sites for single attacks; also communicability was the best to select a subset of nodes sensitive to lesions (Perm test: $p<0.0014$). In addition, communicability related metrics were found to be more sensitive to random edges lesions and local changes were found also in regions distant from the focus of the lesions.

Discussion: Communicability is a wider measure of connectivity based on the idea that all the paths connecting two nodes contribute to the information flow ([3],[4]). Secondary and longer paths may be strengthened in the case of lesions. Our results suggest that communicability related metrics are sensitive to changes in the brain structural network topology in the case of lesions.

## I4 Emotional Rivalry: Homeostatic Emotions are Prioritized over Competing Sensory Emotions

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The ability to experience a wide variety of emotions is a fundamental characteristic of mankind. Hunger for food, air, and fluids (i.e. thirst) are examples of homeostatic emotions crucial for human survival, while sensory evoked emotions, such as anxiety and disgust, improve survival prospects when confronted with specific circumstances. In daily life, homeostatic and sensory emotions can be experienced simultaneously, which leads to an emotional conflict. We investigated the behavioural consequences of this emotional rivalry and its neurobiological underlying in subjects who experienced thirst (homeostatic emotion) and disgust (sensory emotion) at the same time. After 18 hours of water deprivation 20 healthy subjects underwent functional MR imaging. BOLD fMRI was measured during an intense thirst phase and after drinking to satiation. Both during thirst and satiation two odour stimuli (1 disgusting, 1 pleasant) were presented to the subject inside the scanner in an event related paradigm. Subjects rated both odours for pleasantness and intensity. For the fMRI data

analysis a two-stage mixed effects model was calculated: At single subject level, we estimated the parameters of a GLM that included the odour stimulation during both hydration states. These parameter estimates were subsequently used in a random effects analysis, which was performed to identify disgust-related brain regions and brain areas related to the interaction between thirst and disgust. Comparing the odour ratings of the two hydration states, we found that the disgusting odour was rated as less repulsive in the thirsty condition, whereas no difference was found for the positive odour. The disgusting odour stimulation elicited neural activation in well-known disgust related brain areas, mainly in the anterior insula bilaterally. In the thirsty condition, this disgust- related activity was reduced in the left insular cortex. These results indicate a hierarchical processing of emotions in a situation of emotional rivalry: the homeostatic emotion thirst is prioritized, which is vital in terms of natural selection and determining human behavioural responses.

## I5 Inverse correlation between white matter cerebral blood flow and structural connectivity of the human brain

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Introduction: Little is known about white matter perfusion and its relation to structural connectivity. Recently, an inverse correlation between white matter cerebral blood flow (CBF) and structural connectivity was reported on a tract-specific basis [1]. In the present study we present a voxel-wise approach to probe for a relationship between metabolic and microstructural connectivity within white matter across subjects.

Methods: A total of 32 healthy subjects were included in the study (20 - 46 years). DTI was acquired and pre-processed with TBSS [2], part of FSL [3] resulting in fractional anisotropy (FA) maps. Pseudo-continuous ASL sequence was acquired and pre- processed with BASIL [4] part of FSL [3], resulting in CBF maps.

A voxel-wise correlation analysis was performed between FA and CBF within the white matter skeleton over all subjects.

Results: A significant negative correlation (corr $p < 0.05$) was observed between CBF and FA values in the body of the corpus callosum, the right anterior thalamic radiation, the right anterior corona radiata and the forceps minor. Furthermore, a significant positive correlation (corr $p < 0.05$) was found between CBF and radial diffusivity in similar white matter regions.

Conclusions: In line with a previous study on a tract-specific basis [1], we observed a significant relationship between CBF and microstructural properties across subjects. The current findings suggest the possibility that subjects with lower white matter perfusion display higher myelination, lower axonal diameter or more mechanical tightness within fiber bundles [1].

References: [1] Aslan S, et al. (2011) Neuroimage 56: 1145-1153. [2] Smith SM, et al. (2006). Neuroimage 31: 1487-1505. [3] Smith SM, et al. (2004). Neuroimage 23 Suppl 1: S208-219. [4] Chappell MA, et al. (2009). IEEE Transactions on Signal Processing 57(1):223-236.

## I6 Inverse correlation between white matter cerebral blood flow and functional connectivity in resting state networks of the human brain

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Introduction: Little is known about white matter perfusion and its relation to functional connectivity (FC). In the present study we present

a voxel-wise approach to probe for a relationship between FC of resting-state networks (RSN) and white matter perfusion as well as microstructural properties across subjects.

Methods: A total of 32 healthy subjects were included in the study (20-46 years). DTI was acquired and pre-processed with TBSS [1], part of FSL [2] resulting in fractional anisotropy (FA) maps. Pseudo-continuous ASL sequence was acquired and pre- processed with BASIL [3] part of FSL [2]. FC of several RSN was assessed across CBF time-series [4] and fed into voxel-wise statistics to probe its relationship with white matter FA and CBF across subjects.

Results: We observed a negative correlation between FC of the auditory RSN and white matter perfusion across subjects (corr $p < 0.05$). Furthermore, FC within default mode network was negatively correlated with white matter CBF ($p < 0.05$) and positively correlated with FA across subjects ($p < 0.05$).

Conclusion: In line with a previous study on a tract specific basis, we observed an inverse correlation between FC in some RSN and white matter perfusion across subjects [5]. Furthermore, our findings of a positive relationship between FC and white matter microstructural properties are in line with previous findings [6].

References: [1] Smith SM, et al. (2006). Neuroimage 31: 1487-1505. [2] Smith SM, et al. (2004). Neuroimage 23 Suppl 1: S208-219. [3] Chappell MA, et al. (2009). IEEE Transactions on Signal Processing 57(1):223-236. [4] Smith SM, et al. (2009). Proc Natl Acad Sci USA (PNAS), 106(31):13040-13045, 2009. [5] Aslan S, et al. (2011). Neuroimage 56: 1145-1153. [6] Greicius MD, et al. (2009). Cereb Cortex. 19 (1): 72-78.

## I7 Neural correlates of global timing processing in the auditory domain

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Temporal context processing can induce “time warps” in local timing perception. This study aimed to elucidate the neural mechanisms of such interactions between global and local timing perception. Participants performed a duration discrimination tasks in a rhythmic auditory sequence in which the critical interval duration was presented either within a rhythmical group or between two rhythmical groups. From the behavioral performance in the twoalternative forced choice task we estimated the difference limens (DLs) for the critical duration and the points of subjective equality (PSEs). We found that listeners perceived the probed interval duration significantly different in the betweengroups and the withingroup conditions. The PSEs were 450 ms for the betweengroup condition and 391 ms for the within group condition (the objective duration was 400 ms). Furthermore, the DLs of 6.7% and 6.4% respectively were not significantly different indicating that the two experimental conditions were comparable in task difficulty. Functional magnetic resonance imaging (fMRI) indicates that the phenomenon of contextinduced “time warps” is mediated by subcortical and medial frontal cortex activity.

## I8 Modulation of Tonotopic Maps by Focal Brain Lesions: case studies

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The primary auditory cortex (PAC) is central to human auditory abilities, yet its anatomical location remains unclear. In control subjects,

we measured two large tonotopic subfields of PAC (A1 and R) relative to the underlying anatomy of Heschl's gyrus (HG). The data reveals a clear anatomical-functional relationship that indicated the location of PAC across the range of common morphological variants of HG (single gyri, partial or complete duplications). The size and shape of these subfields are proper to each hemisphere and subject. Here, we speculate that A1 and R (but also others non primary subfields) could be modulated by events such as stroke or traumatic brain injury (TBI). Three patients and five healthy controls were scanned at 3T. Subjects listened passively to progressive cycles of pure tone bursts (from 88 to 8000 Hz) presented in blocks of 32 sec during 8 min in ascending or descending runs. First, the largest cluster containing mirror-symmetric gradients centred on HG was extracted manually for each hemisphere and normalised by the total amount of voxels in order to get percentages for each frequencies representations. Second, time courses of each voxel were extracted, normalized and averaged according preferred frequency, resulting in a percent signal change variation for each one of the fourteen presented frequencies. Finally, we computed several statistical analyses between each patient and the control group. We measured maintained tonotopic gradients in ipsi- and contralesional hemispheres, despite relative frequency representations partially altered. Low frequencies tended to be more represented in ipsi- and contralateral primary auditory cortices. Signal change variations for frequencies around the speech spectra were enhanced contralaterally to cerebellar lesion and decreased ipsilaterally to hemispheric lesions. These results could be related to diaschisis-like neuronal plasticity.

## I9 Dorsolateral prefrontal cortex thinning is related to altered functional connectivity with default mode and task-positive networks in major depressive disorder

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Major depressive disorder (MDD) is consistently associated with reduced grey matter volume of the anterior cingulate cortex (ACC), dorsolateral and dorsomedial prefrontal cortex (DLPFC, DMPFC). These structural changes may be particularly relevant to MDD because the ACC/DMPFC and the DLPFC are considered part of the default mode and the task-positive networks (DMN, TPN), respectively, and functional alterations between these two networks have been proposed to play a key role in MDD. However, whether structural changes within this fronto-cingulate circuit are associated with abnormal resting-state functional connectivity (FC) and whether these functional alterations are related to the symptoms' severity has not been investigated yet. Whole-brain cortical thickness was calculated and compared between 21 unmedicated depressed patients and 35 healthy controls. Regions with reduced cortical thickness defined seed regions for subsequent whole-brain FC analyses. Depressed patients showed bilateral thinning of the DLPFC and increased FC of the right DLPFC (R-DLPFC) with the dorsal ACC (dACC) and the orbitofrontal cortex (OFC)/rostral ACC compared to healthy controls. FC of the R-DLPFC with the left middle temporal cortex and that of the left DLPFC (L-DLPFC) with the right motor cortex/supplementary motor area were decreased in patients. Moreover, depression severity positively correlated with FC of the L-DLPFC with the dorsal nexus, even though FC between these two regions was not significantly different between depressed patients and healthy controls. These findings suggest that thinning of the DLPFC in MDD has a key role in the abnormal functional connectivity between the TPN and DMN.

## I10 fMRI with and without EEG, does it make a difference?

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Electroencephalography (EEG) as well as magnetic resonance imaging (MRI) techniques are well established and widely used in the field of clinical and cognitive neuroscience. By bringing together these two imaging methods, one can benefit from both the high spatial resolution of the MRI and the high temporal resolution of the EEG. However, simultaneous EEG and fMRI measurements bring along the challenge of proper artefact cleaning, in particular in the EEG data, namely the MRI-related ballistocardiological and gradient artefacts. In this study, we compared data quality of T1- and T2*-weighted (echoplanar) images at 3 Tesla, recorded with and without a high density EEG cap (256 channels). To figure out whether putative adverse effects on data quality arise from magnetic inhomogenities of the static magnetic field or of perturbations of the radio frequency pulse, B0 and B1 field maps were recorded. As reported in previous studies, we revealed a reduced signal-to-noise ratio for both, the functional and anatomical data when subjects wear the EEG cap in the scanner. To the best of our knowledge we report for the first time significantly altered surface- based morphometry measurements of cortical thickness over frontal and temporal brain regions for simultaneous EEG-fMRI recordings. Analysis of simultaneously recorded fMRI data delivered reliable results, independent of including the individual anatomical image with or without the EEG cap in the spatial normalization step of fMRI preprocessing. A comparison of the anatomical images with and without the EEG cap showed slight edge effects between brain tissue and cerebrospinal fluid. The observed effects fit nicely to the obtained results regarding field inhomogenities of the B1 and B0 map. Taken together, our data reveal a strong sequence-dependent influence on MRI data quality. Based on our findings, we strongly advice to not record anatomical images simultaneously with EEG when there is an additional need or interest to focus on separate anatomical data analysis beside including the individual T1-weighted images in fMRI preprocessing.

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## I11 CUTTING LIKING AT ITS JOINTS: NEURAL PATTERNS OF OLFACTORY EMOTIONS

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Odor perception is a complex process merging sensory input with strong emotional components. While the representation of affective valence has been investigated by previous imaging studies in humans, this dichotomic dimension may not be sufficient to account for the richness of odor-evoked emotions. Here we used fMRI to study how distinct emotional components of odors are represented neurally, beyond valence. 17 Participants were presented with 12 prototypical smells covering the spectrum of olfactory emotions as defined by the 6-level Geneva Odor Emotion Scale (GEOS). Odors were delivered with an MRI compatible olfactometer, and participants performed a simple detection task after each trial. They then rated the pleasantness of the odors, as well as the subjective feelings elicited by them along the GEOS categories at the end of each session. fMRI results showed activations in major olfactory brain structures, including piriform and parahippocampal cortices, amygdala, and hi ppocampus. Orbitofrontal cortex was activated medially by pleasant odors and laterally by unpleasant smells, together with insula, in keeping with past work. We performed parametrical analyses with GEOS and hedonicity scores, in order to identify the substrates for specific dimensions of olfactory emotions and pleasantness, while acknowledging for individual differences in subjective percept. We observed emotion category specific neural profiles, persisting after the removal of

parametric effects due to the valence component. Taken together, these results illustrate the specificity and relevance of the GEOS framework to account for emotional responses to odorants in the brain, as compared with measures based on pleasantness only.

## I12 In vivo characterization of a novel fluorescent pipette coating for targeted single cell physiology

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Targeted in vivo physiology typically relies on soluble fluorescent dyes (e.g. Alexa Fluor) that are added to the internal solution in order to visualize the pipette tip under the microscope. Such dyes have a relatively low optical efficacy for two-photon microscopy and therefore require high laser powers, which can affect brain function. During long recording sessions, fluorescent dye also tends to accumulate in the extracellular space, reducing the visibility of the pipette tip and therefore the efficacy of spatial targeting. We have recently developed a novel method for coating of the external surface of standard borosilicate patch pipettes with hydrophobic fluorescent nanocrystals (quantum dots). This coating allows excellent visualization in brain tissue under two- photon microscopy, yet does not alter the electrophysiological properties of the pipettes (Andrasfalvy et al. 2013, SfN 14/JJJ68). Quantum dots display several optical properties that make them superior to typical fluorescent dyes for two-photon microscopy, such as excellent quantum yield, high resistance to photobleaching and broad absorption with narrow emission spectra. Here we present the characterization quantum dot coated pipettes for in vivo targeted single cell recordings. We used the pipettes to perform whole-cell and cell attached recordings of layer 2/3 neurons expressing the genetically encoded calcium indicator GCaMP6 or ChR2 to calibrate their function. The coated pipette tips can readily be followed to depths below >300 um at low laser powers (<30mW). Although the quantum dots were partially wiped off when penetrating the dura, they did not leave any fluorescent deposit within the brain tissue. Interestingly, during coating the quantum dots were found to accumulate at the tip of the pipette, thereby further facilitating the precise spatial targeting of individual cells. Coating with quantum dots did not affect the electrophysiological properties of the pipettes for whole cell or cell attached recordings, nor did it influence the functional properties of the targeted neurons. Finally, combining external quantum dot coating with internal Alexa Fluor dye allowed us to perform highly efficient and precisely targeted single-cell electroporations, further illustrating the advantages of this novel tool.

## I13 Postural knowledge of gestures in patients with schizophrenia is associated with gray matter volume of the right inferior frontal gyrus and the left hippocampus. Preliminary results of a whole brain voxal based morphometry (VBM) study.

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Background: Schizophrenia patients show impaired gesture performance and recognition. Higher order processes such as recognition of gestures rely on a network of distinct and distant brain areas. Particularly the role of key regions such as the left inferior frontal gyrus

(IFG) and the inferior parietal lobe (IPL) in gesture performance and understanding and recognition is subject to ongoing debate. However, the neural correlates of impaired gesture recognition in schizophrenia patients have not yet been investigated. We therefore aim at investigating the neural basis of impaired gesture recognition in patients with schizophrenia by applying voxel based morphometry and a comprehensive assessments of gesture recognition.

Methode: In total, 19 schizophrenia patients diagnosed according to DSM-5 criteria underwent structural imaging and a comprehensive test for postural knowledge of gestures (postural knowledge task). We explored correlations of performance of postural knowledge and gray matter (GM) volume to voxel-based morphometry (VBM) data with total GM volume as covariates. A statistical threshold of $p < 0.001$, uncorrected, minimum cluster size of 50 voxels, was applied.

Results: The whole brain analysis revealed a main effect of postural knowledge within the right inferior frontal gyrus extending to the insula (MNI-coordinates: x = 36, y = 18, z = 2 and x = 58, y = 2, z = -2; cluster size 836 voxels, T = 7.79) and the left hippocampus (MNI-coordinates: x = -22, y = -16, z = -16; cluster size 102 voxels, T = 7.79).

Discussion: Postural knowledge performance in schizophrenia patients was associated with gray matter volume of two meaningful brain regions - the right inferior frontal gyrus extending to the right insular and the left hippocampus. This is in line with the literature as particularly lesions in the IFG were found to predict poor gesture recognition of any domain in brain damaged patients. Further, Hippocampus volume reduction is one of the most consistent structural abnormalities of schizophrenia patients and is part of a brain system responsible for spatial memory and navigation.

## I14 A correlative light and electron microscopy approach for reconstructing syringeal motor neuron circuits in a songbird

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What are the identities of postsynaptic partners of a given neuron? Correlative array tomography (CAT) is a good candidate to address this question; it consists of imaging hundreds of consecutive ultrathin sections of brain tissue using both light (LM) and electron (EM) microscopy. It combines the strengths of the two imaging modalities, namely fast acquisition and multicolor imaging for LM and nanometer resolution for EM. We further enhanced a CAT protocol previously developed in our laboratory, by allowing the simultaneous visualization of 5 conventional tracers (Biotinylated Dextran Amine,Alexa 488, TexasRed, LuciferYellow and Fluorescein) while preserving excellent ultrastructure for reliable neuron tracing and identification of synaptic contacts. We aim to characterize how cortical and brainstem neurons project to motoneuron pools involved in the production of learned, skilled, and highly stereotyped behaviors. Our model organism is the songbird zebra finch, in which motoneurons controlling the vocal organ are innervated by direct monosynaptic connections from the brainstem nucleus dorsomedialis(DM), as well as from the avian analogue of motor cortex,the robust nucleus of the arcopallium(RA). Light microscopy provides the identity of the structures of interest: fluorescent tracers injected in vivo in the brainstem, in the motor cortex, and in the different muscles of the vocal organ are visualized directly on ultrathin sections. On the same sections, in the electron microscope, we can unambiguously delineate membranes and synaptic contacts. Our approach allows for reconstruction of labeled brainstem and cortical axons over hundreds of consecutive sections and for identification of their synaptic contacts with labeled motoneurons. We hope to determine quantitatively if and to which extent single mesencephalic and corticomotoneuronal cells connect to motoneuron pools innervating the same muscle.

## I15 Electrical source imaging in epilepsy: a comparison of three head models

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Electrical source imaging (ESI) aims at reconstructing the electrical brain activity from scalp EEG. When applied on interictal epileptic spikes (IES), this technique is of great interest for identifying the irritative zone in partial epilepsy. Forward modelling errors may strongly influence ESI and lead to mislocalization of IES generators. In this context, head models used for solving the EEG forward problem have been greatly enhanced these last 20 years. Currently, the boundary element model (BEM) and the finite element model (FEM) are the most commonly used. However there is a lack of study comparing their accuracy especially in a clinical context.

We propose here to do this study using a dataset of 38 epileptic patients who have undergone high-density scalp EEG, intracranial EEG and surgery. We compared ESI accuracy resulting from BEM, FEM and the less time-consuming local spherical model with anatomic constraints (LSMAC) with respect to intracranial recordings and surgical resection. All of them were computed from individual MRI and ESI was performed on averaged IES.

We found that all head models provided very similar ESI. For patients having a positive post-operative outcome, at least 74% of maximum ESI were in the resection. The median distance from maximum ESI to the nearest intracranial electrode showing IES was 13.2, 15.6 and 15.6 mm for LSMAC, BEM and FEM, respectively. We think that in clinical applications, unavoidable errors such as MRI noise, EEG noise, and mislocation of electrodes, minimize the influence of the choice of the head model. The use of highly sophisticated head model is then not a crucial factor for an accurate ESI.

## I16 Connectivity-based neurofeedback: dynamic causal modeling for real-time fMRI

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Neurofeedback based on real-time fMRI is an emerging technique that can be used to train voluntary control of brain activity. Such brain training has been shown to lead to behavioral effects that are specific to the functional role of the targeted brain area. Recent studies even demonstrated therapeutic effects in specific patient populations. However, real-time fMRI-based neurofeedback so far was limited to training localized brain activity within a region of interest. Here, we overcome this limitation by presenting near real-time dynamic causal modeling in order to provide neurofeedback information based on connectivity between brain areas rather than activity within a brain area. Using a visual-spatial attention paradigm, we show that such a connectivity feedback signal can be used to train voluntary control over functional brain networks. Because most mental functions and most neurological disorders are associated with network activity rather than with activity within a single brain region, this novel method is an important methodological innovation in order to more specifically target such brain networks.

## I17 Functional neuro-anatomy of egocentric versus allocentric representation

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The functional neuroanatomy of the egocentric and allocentric representations of space remains poorly studied with neuroimaging. Here we aim to determine brain structures subserving two different kinds of spatial representations centred on the main axis of either the body or the external scene. Sixteen healthy participants evaluated the alignment of a bar relative to the middle of their body (Ego) or relative to another stimulus (Allo) during functional MRI. In a control task (Ctrl), they had to judge the colour of the bar. The correct response rates and response times were similar in the three tasks. fMRI data revealed a predominant role of the right hemisphere in the egocentric task (Ego vs. Allo): selective activity was found in the occipital, superior parietal, and inferior frontal cortices, as well as in the precuneus and supplementary motor area. On the left side, the insula, thalamus, and cerebellum were also activated. Conversely, the allocentric task (Allo vs. Ctrl) showed selective activity centred on the left temporal gyrus. This study demonstrates a right hemisphere dominance for representations centred on the longitudinal body axis, but more left-sided activity for scene/object-centred representations of space. These new data shed light on the unique role of several regions involved in spatial perception and help better understand spatial deficits in patients with right hemispheric lesions.

## I18 The interactive role of the Medial Temporal Lobe explains personal probabilistic learning

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Recent models of memory systems highlight that to understand the functions of Medial Temporal Lobe (MTL) regions it is necessary to identify the interaction with other memory nodes in the brain (Poldrack et al., 2001). Multiple cues probabilistic learning offers a way to probe the different memory systems. We hypothesize segregated but interacting systems underlying individual learning and memory components: hippocampus (episodic memory), fusiform gyrus (perceptual memory), pre-frontal cortex (working memory) and basal ganglia (BG) (procedural memory). In our 3D game, the participants had to learn, based on feedback, the probabilistic association between combined cues (pseudo-letters) and a binary outcome. There are 2 strong (20% and 80%) and 2 weak (40% and 60%) predictive cues. We acquired EPI images in a 3-Tesla Siemens scanner (TR 2 s, 3mm3 resolution) on 2 sessions of 280 trials. We use rolling logistic regression to infer the trial-by-trial utilization weights of each cue based on subject's choice (Kelley et al., 2002). Bilateral caudate nuclei had greater activation during learning trials compared to baseline in. In contrast, bilateral hippocampi and parahippocampal cortices showed activation decrease during learning trial. Inferior occipito-temporal, right mid/inferior frontal cortex and insula activation was predicted by the cue utilization weight for the four cues. We interpret our results as evidence for of a cross-talk between different memory systems for optimal learning (Seger et al., 2010; Henke et al., 2010) with top-down influences from the higher level region (frontal cortex) to low level regions (LOT) (Kherif et al., 2011).

## I19 The influence of sodium oxybate and sleep on reward processing: an fMRI study

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Sodium oxybate (SO; Xyrem®) has been approved in most countries for treatment of narcolepsy with cataplexy. It acts as a GABA(B) receptor agonist, improving disrupted sleep, decreasing sleep onset latency, and increasing slow waves sleep (SWS) in narcoleptic patients as well as in healthy subjects. Here, we tested (1) whether SO influences brain network related to reward processing and (2) whether changes in sleep induced by SO affects reward processing in healthy subjects on the next day.

Nineteen subjects were given SO or placebo (PL) over 2 distinct fMRI sessions. Each subject performed a game-like task, before and after SO/PL administration in an evening session. PSG was recorded in the following night. On the next day, one more session of game-like task was performed during the afternoon. During the game-like task, subject could win or lose points by rapidly detecting a target. We compared brain activity during winning or losing points after SO or PL, during the evening session and after the sleep.

At behavioural level, subjects detected the target more rapidly after negative cues (potential losses) immediately after SO, suggesting that they mainly want to avoid losing points. Subjects also often pressed too early under SO for positive cues (potential gains), suggesting increased impulsivity for obtaining rewards. After one night sleep, we observed no modification in reaction times after SO or PL.

At the fMRI level, during the evening session, we observed that subjects under direct influence of SO (as compared to PL) showed significant activation in an error monitoring network (including the anterior cingulate) when they are losing, and activated significantly more a network related to reward processing (including the striatum) when they are actually winning, suggesting that SO also enhance the sensation of positive reward. After a night of sleep modified by SO (vs PL), we found a significant activation of the bilateral amygdala and right insula when subjects lose a large amount of points, suggesting that changes in sleep after SO administration may have an effect on error processing and emotional reactivity on the next day. SO (as compared to PL) influences reward functions at both the behavioral and brain levels.

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## I20 3D Analysis of Neuronal Ultrastructure

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In recent years serial block face scanning electron microscopy has transformed the way neuroscientists approach the daunting task of studying neuronal morphology and connectivity. Here we show how this method for automatically generating aligned serial images through volumes of tissue and at different length scales can be used to analyse cell structure. We present how the latest computer programs are able to accurately segment and reconstruct different features and how a newly developed software tool can be used to make details measurements of these objects in 3D space. These advances are transforming ultrastructural studies, making them faster, and more accurate. Additionally they provide the opportunity to correlate light microscopy imaging with electron microscopy without the need for immunocytochemistry ensuring optimal structural preservation.

## I21 Magnetic resonance spectroscopy investigations of functionally defined language areas in schizophrenia

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Background: Cerebral dysfunction in mental disorders may be associated with metabolic disturbances that are limited to circumscribed brain areas. Auditory hallucinations have been shown to be related to defined cortical areas linked to specific language functions. Here, we investigated if the study of metabolic changes in auditory hallucinations requires a functional rather than anatomical definition of their location and size to allow a reliable investigation by magnetic resonance spectroscopy (MRS).

Methods: Schizophrenia patients with (AH; n=12) and without hallucinations (NH; n=8) and healthy controls (HC; n=11) underwent a verbal fluency task in functional MRI (fMRI) to functionally define Broca's and Wernicke's areas. Left and right Heschl's gyrus were defined anatomically.

Results: The mean distances in native space between the fMRI-defined regions and a corresponding anatomically defined area were 12.4±6.1 mm (range: 2.7-36.1 mm) for Broca's area and 16.8±6.2 mm (range:4.5-26.4 mm) for Wernicke's area, respectively. Hence, the spatial variance was of similar extent as the size of the investigated regions. Splitting the investigations into a single voxel examination in the frontal brain and a spectroscopic imaging part for the more homogeneous field areas led to good spectral quality for almost all spectra. In Broca's area, there was a significant group effect ($p = 0.03$) with lower levels of N-acetyl-aspartate (NAA) in NH compared to HC ($p = 0.02$). There were positive associations of NAA levels in the left Heschl's gyrus with total ($p = 0.03$) and negative ($p = 0.006$) PANSS scores. In Broca's area, there was a negative association of myo-inositol levels with total PANSS scores ($p = 0.008$).

Conclusion: This study suggests that a functional definition of regions to be investigated by MRS is needed if neurochemical imbalances are expected to be restricted to functional foci. The neurochemical results do not support the neurodegenerative hypothesis of schizophrenia.

## I22 The sound (and pitch) of silence: experience-based auditory predictions modulate the spatio-temporal brain processing of omitted sounds

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Current evidence indicates that behavioral and brain responses to sounds do not solely depend on the acoustic features of incoming stimulation, but on the interaction between incoming stimuli and internal forward models anticipating upcoming information based on previous experience. By investigating brain responses to expected but omitted sounds, auditory forward models can be characterized free of contamination by actual stimulation. In the current study, we examined the spatio-temporal dynamic of electrical neuroimaging responses to omitted sounds presented in a rule-based sequence of tones with varying pitch. Within the sequence, the inter-stimulus interval was kept constant and the succession of the different pitches followed a simple rule, respectively ensuring that the onset time and the pitch of the forthcoming sounds were predictable. Exposure to the sequence thus enabled participants to rapidly build up an internal forward model of when and which sound would be presented. To test the effects of attention on the forward model, two groups of participants listened to the sound sequences either passively or actively. We investigated the temporal dynamics of the effects of the forward model on auditory brain processes using data-driven time- frame wise statistical topographic analyses of the ERP time-locked to the expected onset of the omitted sounds. In both active and passive listening conditions, topographic consistency tests revealed ERP signals significantly different from noise at 120-200 ms and 290-320 ms after the (expected) onset of the omitted tone. A two by three

topographic mixed ANOVA with factors Listening condition (Active; Passive) and Expected pitch (High; Medium; Low) revealed a main effect of pitch at 140-200 ms after the onset of the omitted tone, indicating that the expected pitch of the omitted tones modulated the configuration of the brain networks responding to the omission. There were no main effects of factor Listening condition nor interactions. Collectively, these results indicate that even in the absence of any stimulation, internal forward models have a critical impact on the processing of incoming auditory information by modulating cortical activity over early, low-level 'sensory' processing stage, to match not only the anticipated presence of a sound, but more specifically its expected pitch.

## I23 Dynamics of directed information transfer in visual processes

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Visual stimuli quickly evoke processing in a network of primary visual and higher-level brain areas, giving rise to dynamic interactions between them that are poorly understood. Here we investigated directed interactions in visual processing via time- varying Granger-causal modeling. Using fMRI we localized in each subject six regions of interest (ROI) in each hemisphere: primary visual cortex, lateral occipital complex, fusiform gyrus, area MT+, lateral intraparietal sulcus and the frontal eye field. In a separate EEG session subjects performed a target detection task on the center of the screen while we briefly presented checkerboards in the lower left and right visual field. From the EEG we estimated time-series of activity in each ROI using a distributed linear inverse solution (WMN) and realistic individual head-models. With adaptive MVAR modeling we then derived the directed influence between all ROIs in time, scaled by the instantaneous spectral power (wPDC). The results show peak driving from primary visual cortex at expected latencies. Predominant driving from parietal areas was observed in the alpha band, whereas in the gamma band driving from MT+ was most pronounced. The work demonstrates the potential for studying directed interactions between brain areas in visual processing by combining EEG source imaging and wPDC.

## I24 Neural Correlates of Passive Forefinger Kinematics: A robotics and neuroimaging approach

**Authors**

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While the differential neural responses to passive and active movements have been well-studied, there is little understanding as to the relationship between the degree of passive movement and brain activity. Afferent input includes receptors that are sensitive to both length and rate of length changes in the musculotendon unit. Thus, we hypothesized that these parameters are represented differently in the brain during passive forefinger movement. We measured whole brain blood oxygenation level dependent (BOLD) signal using functional magnetic resonance imaging (fMRI) in response to parametric changes in passively induced forefinger kinematics. Nineteen healthy participants were exposed to combinations of forefinger flexion and extension imposed by a MR-compatible robotic manipulandum which also measured forefinger interaction forces. Each subject was exposed to passive forefinger movements at three different levels of amplitude and velocity, separately in flexion and extension. We used a parametric analysis and modeled forefinger interaction force as a regressor of no interest to account for variance due to different mechanoreceptor input. We found that contralateral primary and

secondary somatosensory regions, as well as putamen and ipsilateral cerebellum positively correlated with increases in kinematics, in agreement with previous studies involving active movements. We also observed a difference in sensitivity between the regions. These results will provide a model for a greater understanding of the neural representation of kinematic variables, and will inform the design of future brain-machine interfaces.

## J. Disorders of the Nervous System: Basic Mechanisms

### J1 Implication of sperm RNAs in the inheritance of the effects of early traumatic stress in mice

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Stressful experiences during early life constitute a major risk factor for the development of neuropsychiatric disorders in adulthood and across generations. We are investigating the transgenerational transmission of the impact of early stress on behavior and metabolism, and its underlying mechanisms in a mouse model of postnatal traumatic stress. This model is based on unpredictable maternal separation and maternal stress (MSUS) and expresses impaired risk assessment on the elevated plus maze, lower anxiety in the light dark box test, and depressive behaviors on the forced swim test that are transmitted across generations. It also has inherited metabolic dysfunctions. This study examines whether small RNAs in sperm contribute to the transfer of these behavioral and metabolic traits across generations. It shows that postnatal traumatic stress alters miRNAs expression in several tissues and cells including brain, serum and male germ cells in mice. The progeny of MSUS animals express comparable miRNAs alteration in the brain, suggesting transgenerational transmission. Injection of sperm RNAs from MSUS males into fertilized mouse oocytes reproduces the behavioral and metabolic symptoms. These results suggest that sperm RNAs are likely contributors to the expression and inheritance of the effects of early stress on behavior and metabolism. They offer novel mechanistic perspectives and possible diagnostic tools for the detection of a predisposition to stress in humans.

### J2 Delayed repeated treatment with baclofen promotes neuronal plasticity and functional recovery after stroke in rats

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Introduction: Stroke remains one of the leading causes of death worldwide, but no effective treatment is available for the patients. Promotion of neuroplasticity during stroke recovery may represent an alternative therapeutic strategy. Several studies have suggested that neuronal plasticity can be facilitated by sleep. We investigated stroke outcome following delayed repeated treatment with baclofen (Bac) in a rat model of focal cerebral ischemia (isch).

Methods: 24h after initiation of focal cerebral ischemia (permanent occlusion of the distal branches of middle cerebral artery, MCAo) rats were treated with Bac (10 mg/kg) or saline. Then injections were performed twice daily during 10 consecutive days. Three groups of rats were designed: isch/Bac, sham/Bac and isch/saline. Sleep was assessed by EEG recordings, sensorimotor function by single pellet reaching

test (SPR) and axonal sprouting by biotinylated dextran amine (BDA) tracing. Results: Repeated Bac treatment after MCAo affected sleep, brain plasticity and motor function. NREM sleep amount was increased significantly during the dark phase in isch/Bac compared to the isch/saline group ($p<0.05$, unpaired t-test; days 2, 6 and 11). SPR performance dropped to 0 immediately after MCAo in both ischemic groups and recovered slowly thereafter. No significant difference in reaching was found between isch/Bac and sham/Bac groups 33 days after MCAo. In contrast, isch/saline rats never attained the level of sham group and performed significantly worse than isch/Bac rats ($p=0.01$, Tukey-Kramer). The BDA stained areas of the ipsilesional motor cortex and striatum were larger in the ischemic group treated with Bac ($p<0.0001$, Tukey-Kramer). Bac had no effect on the size of the brain damage.
Summary: Our data indicate that delayed repeated Bac treatment might promote neuronal plasticity after stroke and thereby benefit motor function recovery. Observed effects might be mediated by sleep.

## J3 Spontaneous locomotor activity and L-DOPA induced dyskinesia are not linked in 6-OHDA parkinsonian rats

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Locomotor disorders like bradykinesia or hesitation of gait initiation are a hallmark of Parkinson's disease (PD). Levodopa (L- DOPA) remains the most effective option in the treatment of PD. However, most of the parkinsonian patients under L-DOPA therapy develops "ON/OFF" motor fluctuations, and abnormal involuntary movements (AIMs) called dyskinesia. The purpose of our study is to better understand whether the motor responses are linked with the development of dyskinetic movements. We characterized an animal model of PD suitable to mimic the motor disorders developing in humans "before", "during" and "after" L-DOPA therapy and we correlated the severity of dyskinetic movements (AIMs scores) to the locomotor response in "ON/OFF" phases of chronic L-DOPA treatment. For this study, we used three parkinsonian animals groups treated with chronic injections of L-DOPA 8mg/kg, 6mg/kg and Saline, respectively and one group of "Naive" animals receiving L-DOPA 8mg/kg. The motor activity of all groups was evaluated by Open Field test (OPF) at several phases of L-DOPA treatment and the rats were also rated for dyskinetic AIMs during the chronic treatment. Parkinsonian rats improved their locomotor activity during L-DOPA "ON" phase and interestingly, the rats treated with L-DOPA 8mg performed a higher motor response than the animals treated with a lower dosage, although the development of dyskinetic movements was similar between the two groups. The dyskinetic movements were not linked with the motor responses in "ON" and "OFF" phases of L-DOPA treatment, but only the rotational AIM was correlated with the locomotor activity in the "ON" phase of L-DOPA treatment. We conclude that neural mechanisms leading to dyskinesia are not the same than the ones mediating the spontaneous motor activity at different dosages of treatment. In addition the OPF test proves to be an accurate methodological approach to assess the behavioral responses which are close to the motor disturbances in humans.

## J4 Striatal NMDA receptors and Parkinson's disease

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The main feature of early Parkinson's disease (PD) is the degeneration of the dopaminergic cells in the Substantia Nigra pars compacta (SNC). This leads to a functional impairment of the cortico-basal ganglia loops including glutamatergic pathways. Several studies have described changes in glutamatergic N-methyl-D-aspartate (NMDA) receptors (NRs), expressed in the striatum. However, it is not yet clear

whether this reflects unspecific short-lasting changes or rather long-term adaptations. Our hypothesis is that NRs changes are due to long-term adaptive mechanisms of the corticostriatal pathway and we have, thus, also analyzed the presynaptic corticostriatal glutamatergic system. We used the unilateral 6-hydroxydopamine (6-OHDA) rat model of PD and control animals. Four weeks after the lesion, animals were killed and their brain extracted. We performed in situ hybridization histochemistry with DNA oligoprobes for NRs subunits, in the striatum and for corticostriatal pathway marker (vesicular glutamate transporter 1 (vGluT1)), in the primary motor cortex (M1). Level of gene expression was quantified on film autoradiograms. We observed a higher expression of NR1 and NR2A mRNA in the striatum ipsilateral to the lesion in 6-OHDA animals, but no changes were observed with NR2B mRNA. NR2A subunits are more expressed in the striatal direct pathway neurons than in the indirect pathway projecting cells, indicating that the changes observed are specific for the direct pathway. We also found positive and significant correlations between striatal expression of NR1, NR2A and cortical vGluT1 expression, in 6-OHDA animals. In conclusion our findings suggest a secondary lasting increase of NMDA receptor gene expression belonging to the striatal direct pathway neurons and a pathological interaction between these NMDA receptors and the cortical glutamatergic activity after dopaminergic denervation. These specific gene expression changes might reflect adaptive mechanisms specific to PD.

## J5 In experimental pneumococcal meningitis, MMP and TACE inhibitors impair brain injury

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Pneumococcal meningitis (PM) causes high mortality and morbidity. Brain injury from PM is characterized by cortical necrosis and hippocampal apoptosis. Matrix metalloproteinases (MMP) and TNF converting enzyme TACE are proteolytic enzymes and play a critical role in the pathophysiology of PM.

Aim: To evaluate new MMP/TACE inhibitors for their effect on inflammation and brain damage in experimental PM.

Methods: An infant rat model of PM was used where live Streptococcus pneumoniae (serotype 3) were injected intracisternally. The effects of Trocade (n=56) and Ro 32-7315 (n=41) were compared to littermates treated with vehicle (n=92) alone i.e. succinylated gelatin. Therapy started 3 h post infectionem (hpi). At 18 hpi animals developed symptomatic disease and antibiotic treatment was initiated (ceftriaxone). Samples of cerebrospinal fluid (CSF) were used to confirm bacterial titers, measure levels of MMP-2/-9 (gel zymography), myeloperoxidase activity, and TNF, IL-6, IL-1, IL-10, macrophage inflammatory protein-1, and IFN- (microsphere based immunoassay, Luminex). Coronary brain sections were collected and stained (45 µm cryosections, Nissl-staining) for histomorphometric analysis (cortical injury and hippocampal apoptosis).

Results: Trocade (mainly collagenase inhibition) and Ro 32-7315 (TACE inhibition) showed a protective effect on brain injury. Trocade significantly attenuated apoptotic brain injury in the dentate gyrus of the hippocampus compared to animals treated with vehicle (Trocade 3.63±7.89 apoptotic cells per visual field [c/f], n=43 vs. Physiogel® 6.10±8.05 c/f, n=52; $p<0.05$). Treatment with the TACE inhibitor Ro 32-7315 led to an even more pronounced reduction of hippocampal apoptosis to 0.92±1.47 c/f (n=13, $p<0.005$) when compared to controls treated with Physiogel® alone. Trocade improved survival significantly from 62.9% (Physiogel®) to 85.5% ($p<0.01$) while changes in survival rates of animals treated with Ro 32-7315 remained below statistical significance (43.7%). Ro 32-7315 reduced weight loss and CSF levels of TNF and IL-6 while Trocade reduced TNF and IL-1 concentration in the CSF.

Conclusion: MMP and/or TACE inhibition by Trocade and Ro 32-7315, has a protective effect on brain injury and improve clinical and inflammatory parameters in experimental PM.

## J6 Lithium Protects Neurons from Apoptosis in Experimental Pneumococcal Meningitis

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Pneumococcal meningitis (PM) causes high mortality and many survivors suffer from persisting deficits. Histomorphologic correlates include necrosis in the cortex and apoptosis in the hippocampal dentate gyrus. Lithium (Li) influences apoptotic pathways and has a neuroprotective effect in paradigms of acute and chronic neurodegenerative diseases.

Aim: To assess the effect of Li on brain injury in an infant rat model of PM.

Methods: Five days before induction of PM by intracisternal injection of live Streptococcus pneumoniae infant rats received daily 2 to 63 mg/kg lithium chloride (LiCl; n=79) while controls received 0.85% NaCl (n=77). Eighteen hours post infectionem (hpi), antibiotic treatment (ceftriaxone) was initiated and samples of cerebrospinal fluid (CSF) were used to confirm bacterial titer, evaluate Li concentrations, and measure concentrations of TNF, IL-6, IL-1b, IL-10, MCP-1a and IFN-g by microsphere- based immunoassay (Luminex). Animals were sacrificed at 42 hpi after CSF and serum sample collection and the brain harvested. Coronary sections were stained for Nissl substance to quantify cortical injury and hippocampal apoptosis. Li was determined by capillary electrophoresis in CSF and serum samples.

Results: Therapeutically effective serum concentrations of up to 1.38 mM were achieved with a dosage between 20 and 55.25 mg/kg LiCl whereas 63 mg/kg resulted in toxic levels in a few animals with increased mortality (Li range 0.69 – 2.32 mM). Overall, mortality was 32.1% vs. 31.9% in controls (p=ns). Hippocampal apoptosis correlated both with Li serum concentrations ($r=-0.30$; $p<0.05$; n=47) and LiCl dosage ($r=-0.44$; $p<0.01$; n=47). A significant reduction of hippocampal apoptosis from 11.37+/-8.68 to 7.70+/-8.78 apoptotic cells per visual field (30 – 63 mg/kg LiCl; n=31; $p<0.05$) was observed in comparison to controls (n=35), but cortical necrosis was not affected (p=ns). In this sub-group analysis, mean Li serum concentration was 0.46 mM and correlated with CSF Li concentrations at time of sacrifice ($r=0.87$; $p<0.0001$). In CSF samples, the cyto-/chemokines IL-10, MCP-1, and TNF were significantly increased in animals treated with LiCl (n=15) compared to controls (n=20).

Conclusion: Li attenuates apoptotic brain injury in experimental PM.

## J7 Plasticity of dendritic properties of cortical pyramidal neurons in a chronic pain model

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Dendrites are the neuronal structures receiving most of the synaptic contacts and they participate in the integration and transformation of synaptic inputs for the generation of action potentials. In this respect, dendritic passive and active properties play a major role. This study aimed to uncover the properties of the main apical dendrite of layer 5 pyramidal neurons of the anterior cingulate cortex (ACC) of adult mice, a region that is involved in pain perception. Because strong activation of the nociceptive sensory system can potentially result in increased neuronal excitability in cortical areas, we studied the plasticity of dendritic properties in the ACC of a mouse model of chronic pain. Dual whole-cell patch clamp recordings were performed to assess changes in dendritic and somatic properties in a brain slice preparation from a mouse subjected to chronic constriction injury of the sciatic nerve (CCI) and are compared with control conditions (Sham). We studied Na+ and Ca2+ electrogenesis, HCN channels activation as well passive cable properties of layer 5 pyramidal neuron apical dendrites in the ACC. We find that these dendrites, compared to those of the somatosensory cortex, display a prominent Na+ spike

upon dendritic depolarization and marked use-dependent attenuation of back-propagating action potentials. Moreover, we found that in CCI animals HCN channels are functionally down-regulated specifically in the dendrites, leading to exacerbated synaptic integration and ectopic neuronal firing. Thus, the excitability and integrative properties of ACC dendrites are modified in neuropathic pain, which might be relevant for the development of the pathological state.

## J8 Role of Glia in CNS Repair After Stroke

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Glial cells make up almost half of the total cell population of the brain. Microglia form the principal immune cells of the nervous system. They are the first cells to get activated in response to brain injury or disease; their activation can result in neuroinflammation which, in excess, is often detrimental to the brain tissue. However, recent studies have also elucidated novel neuroprotective functions of microglia in both healthy and diseased or damaged brain. Astrocytes, due to their close association with the neurons, also respond rapidly to pathological states of neurons. Both microglia and astrocytes are also known to secrete factors like BDNF and IGF-1. As a lesion model, we applied large photothrombotic lesions of the motor cortex on one side in adult mice. The contralesional, intact corticospinal tract (CST) reacts to the lesion by outgrowth of collaterals in the cervical spinal cord which subsequent cross over the midline to innervate the denervated sidel of the spinal cord. We aimed to investigate whether microglia were involved in this process. BDA tracer was injected into the rat motor cortex of the contralesional, intact hemisphere while a photothrombotic lesion was induced to motor cortex in the opposite hemisphere. Animals were sacrificed 2,4,6 and 8 days after the stroke and processed for staining for BDA traced fibres as well as for the glial markers IBA-1 for microglia or GFAP for astrocytes. Surprisingly, fine calibre labelled CST fibers, sometimes with growth cone-like struktures at their end, could be seen streaming into the dorsal commissure prominently of the cervical spinal cord as early as 2 days after the stroke. The number of midline crossing fibers was significantly higher at 2 days p.o. Microglial cells were strongly activated at this time point in the denervated half of the spinal cord, interestingly more in the grey than in the white matter, suggesting that the degeneration of the terminal axons initiates an earlier microglial response than the degeneration of the main axons in the CST. Activation of astrocytes as reflected by GFAP immunostaining intensity lagged behind the microglial reaction and was prominent only from day 4 on. Results from these experiments will be used to determine the molecular mechanisms which induce growth in intact adult CST fibers and attract the sprouts across the midline into the denervated former CST target regions.

## J9 ASIC1a contributes to AMPA receptor plasticity following ischemia and acidosis in hippocampal CA1 neurons

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The CA1 region of the hippocampus is particularly vulnerable to ischemic damage. Excitotoxicity in this region is thought to be exacerbated by two forms of post-ischemic AMPA receptor (AMPAR) plasticity – namely, anoxic long term potentiation (a-LTP), and a delayed increase in the prevalence of Ca2+-permeable AMPARs (CP-AMPARs). The acid-sensing ion channel 1a (ASIC1a) is highly expressed in CA1, where it contributes to physiologically induced LTP. Moreover, ASIC1a-dependent toxicity is known to contribute to post-ischemic neuron death.

This raises the question - does ASIC1a activation drive the post-ischemic AMPAR plasticity that plays a crucial role in cell death of anoxic CA1 cells? We have tested this by examining organotypic hippocampal slice cultures (OHSCs) exposed to oxygen glucose deprivation (OGD), and hippocampal pyramidal neurons (HPN) in dissociated culture exposed to low pH (acidosis). We find that a-LTP and the increase in GluA2-lacking calcium permeable AMPARs are both dependent on ASIC1a activation during ischemia. Indeed, acidosis alone is sufficient to induce the increase in CP-AMPARs. We also found that inhibition of ASIC1a channels circumvents any potential neuroprotective benefit arising from block of CP-AMPARs. Our results indicate that ASIC1a activation contributes to post-ischemic AMPAR plasticity, identifying a causal link between acidosis and excitotoxicity in hippocampal CA1 cells.

## J10 Neuroprotective role of umbilical cord-derived mesenchymal stromal cells in a rat model of encephalopathy of prematurity

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Background: Premature birth is a major cause of neonatal morbidity and mortality. Although improvements in perinatal and neonatal care reduce mortality, morbidity remains a serious challenge. Survivors of premature birth will confront enormous neurological problems. Transplantation of mesenchymal stem cells and treatment of ischemic brain injury has been shown to be effective in animal models. This is mainly due to the great plasticity of the neonatal brain and to the secretomes of the cell graft. Wharton`s jelly-derived mesenchymal stem cells (WJ-MSC) are of special interest. These cells have a low immunogenicity and also possess immunoregulatory properties.
Materials & Methods: This study investigates WJ-MSC`s effect in a rat model of severe encephalopathy of prematurity in a sham controlled design. On postnatal day 3, intraperitoneal injection of LPS from E. coli followed by ligation of the left carotid artery and hypoxia (8% O2, 65min) was performed on anesthetized rats. We performed transplantation of human WJ-MSC (250000 cells) using a stereotactic frame on postnatal day 6. The neuroprotective potential of the transplant and mechanisms involved were evaluated using histology and immunohistochemistry on postnatal day 11.
Results: In non-treated animals, the induced brain injury was characterized by extensive microglial activation. Astrogliosis and neuro-axonal impairment was predominantly in the inner layers of the neocortex. This injury was also associated with myelination deficiency. WJ-MSC significantly reduced the extent of the induced brain injury. We detected decreased microglial activation with significant numbers of restored neurons and oligodendrocytes.
Conclusion: Our data strongly suggest the WJ-MSC`s neuroprotective potential in the rat model of encephalopathy of prematurity. The WJ- MSC`s mode of action involves the secretion of neurotrophic factors and the consecutive suppression of the neuroinflammation following the hypoxic-ischemic brain injury.

## J11 Disturbed excitation-inhibition balance in a human embryonic stem cell-derived model for Tuberous sclerosis

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Mutations in the TSC2 gene coding for tuberin, a negative regulator of mTORC1, lead to mTORC1 hyperfunction and to Tuberous Sclerosis, characterized by cortical tuber formation, epilepsy and autism. From transgenic mouse models we know that TSC1 or TSC2 deletion results not only in brain malformations and seizures, but also in altered synaptic plasticity and disturbed learning and memory. To investigate the impact of TSC2-deletion directly in human neurons we used zinc-finger mediated genome editing to target the TSC2 gene in hESCs. After generating hESC clones with heterozygous or homozygous deletions of TSC2, cells were differentiated into neural stem cells and synaptically connected neuronal networks within 6-8 weeks in vitro. TSC2-deletion induced a hyperactivation of mTORC1 and increased protein translation as indicated by hyperphosphorylation of S6 and 4EBP1. To investigate synaptic transmission we used whole-cell patch-clamp recordings, demonstrating that networks of human TSC2-/- neurons show a ~3-fold higher frequency of spontaneous synaptic currents compared to human control neurons. Similarly, the total synaptic charge was ~3-times larger. Recording miniature glutamatergic and GABAergic synaptic currents in the presence of TTX revealed that the excitation-inhibition balance was significantly changed with a 4-fold decrease in the rate of glutamatergic and a 7-fold increase in the rate of GABAergic synaptic currents. By contrast, kinetic properties of GABA and glutamate receptors as well as the amplitude of mEPSCs and mIPSCs appear to be unchanged. Taken together, TSC2-deletion disturbs synapse formation and excitation-inhibition balance in immature human neuronal networks.

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## J12 The putative role of parvalbumin in Autism Spectrum Disorders

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Autism spectrum disorders are largely neurodevelopmental disorders with a strong genetic component characterized by impairments in social interaction, communication and stereotyped patterns of behavior. Genes associated with autism (neuroligins, shanks) encode proteins involved in processes of synaptic formation, maturation and plasticity. The dysregulation of this activity-dependent signaling may be an important component of the molecular basis of ASD, but alternative explanations must be considered, such as an impairment of neurotransmission. In this scenario, interneurons play a key role in the maintenance of the global balance of activity in cortical networks. In particular, the number of fast-spiking interneurons (FSI) expressing the calcium-binding protein parvalbumin (PV) has been reported to be decreased in different well-assessed mouse models of ASD. According to the current view, this decrease in PV-immunoreactive (PV-ir) cells is due to a “loss” of PV- expressing FSI, leading to a change in the E/I balance that may be related to ASD. Yet, the putative “loss” of PV-ir neurons in ASD mice models might be the result of a reduction in PV expression or synthesis. Of interest, PV-deficient mice (PV-/-) show ASD-like symptoms as reported in other “canonical” ASD mouse models. Here, we set out to determine whether the number of “PV FSI” is altered in PV-/- mice using stereological methods. Initial results indicate the number of “PV-interneurons” is not altered in PV-deficient mice. Thus, a mere down-regulation of PV affecting the spatiotemporal aspects of FSI intracellular Ca2+ signals appears to be sufficient to precipitate in an ASD-like behavioral phenotype.

## J13 Functional regeneration of intraspinal connections in vitro

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Adult higher vertebrates have a very limited potential to recover from spinal cord injury. Recently, evidence emerged that intraspinal connections play an important role in the enhancement of functional recovery after spinal cord lesions. Therefore, we aimed for the development of a representative in vitro model of these connections. Our model is based on two organotypic spinal cord slices of embryonic rat, cultured next to each other on multi electrode arrays (MEA). The cultures grow and, within a few days in vitro (DIV), fuse along the sides facing each other. When recording the network activity with the MEA we find a highly synchronized activity pattern between the two slices. We assessed the functional recovery potential of the cultures by calculating the amount of synchronized activity bursts after performing complete lesions through the “fusion site”. Cultures lesioned at a young age (8-11 DIV) retained the high regeneration ability of embryonic tissue whereas cultures lesioned at later stages (>19 DIV) showed a distinct reduction of synchronized activity. Therefore, we conclude that spinal cord slice cultures follow a physiological timeline regarding the regeneration ability of neuronal connections and represent the state of adult tissue after about three weeks in vitro. By using immunohistochemical stainings we studied what kinds of neurons play a role in the reconnection between the two slices. We can exclude the involvement of dorsal root ganglion neurons. In contrast, we identified axons from motor neurons crossing the lesion site. To what extent these axons contribute to functional regeneration remains to be investigated.

## J14 Paracrine factors promote neurogenesis in the adult rat brain

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Endothelial progenitor (EPC) cells have been used successfully for neovascularia-tion approaches both in animal models and in patients. Importantly to note, EPCs mediated effects were identified to be mainly due to the secretion of angiogenic growth factors. The two neurogenic niches in the adult brain are closely associated with vasculature and it has been shown that the local vasculature influences proliferation and migration of neural stem cells. We thus hypothesized that conditioned medium from EPC (EPC-CM) promotes neurogenesis in the subventricular zone of the lateral ventricle wall and in the dentate gyrus of the hippocampus. CM was harvested from EPC cultured under hypoxic conditions and infused in the lateral ventricle of adult rats. One week later rats were sacrificed and the brains processed for histological analyzes. Brain sections were stained for doublecortin (DCX) a marker for neuronal precursor cells. In the subventricular zone, DCX positive cells were found on the infusion side as well as on the contralateral side. Treatment with EPC-CM resulted in a significant increase in the number of DCX positive cells in the subventricular zone particularly in the dorsolateral part of the lateral ventricle as compared to the control group. Similarly, DCX positive cells could be detected in the dentate gyrus on both sides of the brain. In all areas analyzed, the number of DCX positive cells was significantly higher in the EPC-CM treated group as compared to the control group. Taken together, our findings demonstrate that intracerebroventricular administration of EPC-CM increases the number of neuronal progenitors in both neurogenic niches of the adult rat brain. These observations may offer new therapeutic approaches for neuropathological conditions of the brain.

## J15 Expression of Cocaine-Evoked Synaptic Plasticity by GluN3A-Containing NMDA Receptors

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Drug-evoked synaptic plasticity in the mesolimbic dopamine (DA) system reorganizes neural circuits that may lead to addictive behavior. The first cocaine exposure potentiates AMPAR excitatory postsynaptic currents (EPSCs) onto DA neurons of the VTA but reduces the amplitude of NMDAR-EPSCs. While plasticity of AMPAR transmission is expressed by insertion of calcium (Ca2+)-permeable GluA2-lacking receptors, little is known about the expression mechanism for altered NMDAR transmission. Combining ex vivo patch-clamp recordings, mouse genetics, and subcellular Ca2+ imaging, we observe that cocaine drives the insertion of NMDARs that are quasi-Ca2+-impermeable and contain GluN3A and GluN2B subunits. These GluN3A-containing NMDARs appear necessary for the expression of cocaine-evoked plasticity of AMPARs. We identify an mGluR1-dependent mechanism to remove these non-canonical NMDARs that requires Homer/Shank interaction and protein synthesis. Our data provide insight into the early cocaine-driven reorganization of glutamatergic transmission onto DA neurons and offer GluN3A- containing NMDARs as new targets in drug addiction.

## J16 Down-regulation of Shank3 in the VTA impairs postnatal maturation of excitatory synapses onto DA neurons.

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Shank3 is a scaffolding protein of the postsynaptic density that plays a critical role in orchestrating glutamatergic receptors at excitatory synapses. Functionally, Shank3 links group I mGluRs (mGluR1 and mGluR5) to NMDARs and AMPARs through its interaction with Homer proteins and regulates both synaptic transmission and plasticity. In the ventral tegmental area (VTA), mGluR1 function is required for driving postnatal maturation of excitatory transmission but the role of Shank3 is unknown. Here we show that in vitro manipulation of the Shank-Homer interaction impairs the mGluR1-driven switch of NMDAR subunit composition at excitatory synapses onto dopamine (DA) neurons of the VTA. In order to evaluate the role of Shank3 in the VTA in vivo, we knocked down all the major isoforms of the gene in neonatal mice. We performed whole cell path clamp technique of DA neurons in acute midbrain slices and characterized excitatory transmission at juvenile synapses. We observed that downregulation of Shank3 during the critical period of development disrupts postnatal maturation of both AMPARs and NMDARs. Haploinsufficiency of Shank3 in human is one of the most prevalent causes of autism spectrum disorders (ASDs), neurodevelopmental pathologies characterized by impaired social interactions. Since knocked down of Shank3 specifically perturbs the postnatal development of DA neurons, our manipulation would possibly lead to impairment in social behaviours.

## J17 Fine motor control affected by transient inactivation of primary motor cortex using repetitive transcranial stimulation

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The primary motor cortex (M1) plays an important role in the execution of complex behavioral tasks requiring coordinated movements of arm and hand muscles. The aim of the present study is to assess the role played by M1 hand area in the performance of a manual dexterity task involving a synergic action of proximal and distal muscles called the “reach and grasp” drawer task, before and after a transient inactivation of M1 using repetitive transcranial magnetic stimulation (rTMS). We analysed several aspects of motor parameters: first, the temporal unfolding of the task, second, the continuous recordings of the force needed to grasp the button of the drawer (grip force) and the force needed to open the drawer against adjustable levels of resistance (load force), third, the electromyographic (EMG) activity of eight arm and hand muscles and finally, the acceleration in three dimensions of the movement of the hand. To specifically inactivate the area of M1 involved in hand movements, we defined M1 hand region where single pulse of TMS stimulation elicited motor evoked potentials (MEP) with the largest amplitude and the highest probability, and we applied series of burst (3 pulses with 33.3 ms time interval) during 33.3 seconds corresponding to the theta burst stimulation. Preliminary results show a pronounced decrease of EMG activity of hand and arm muscles associated with a decrease of grip and load forces needed to perform the “reach and grasp” drawer task at higher level of resistance to the opening and robust changes of acceleration during the displacements of the hand to perform the task. In future studies, the inactivation of other premotor areas also involved in the control of manual dexterity, such as the premotor cortex and the supplementary motor area should assess the exact implication of those areas in manual dexterity.

## J18 Functional recovery of manual dexterity in non-human primates following a motor cortex lesion assessed with the Brinkman box task

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Motor and somatosensory cortical areas are densely interconnected and participate together to the motor control, forming the functional sensorimotor system. The primary somatosensory cortex (S1) sends corticospinal projections and somatosensory inputs to the primary motor cortex (M1), contributing to the control of voluntary movements, such as the precision grip. Moreover, the somatosensory system plays a key role in active motor exploration by palpation without visual feedback. After a lesion in M1, the sensorimotor system should therefore be affected in parallel with the motor control itself. Therefore, to assess the integrity of the somatosensory system in a lesional context, the Brinkman box task was developed. It is based on the modified Brinkman board task designed to assess the precision grip in non-human primates and consists of a square board containing 10 vertically and 10 horizontally oriented wells, each filled with a banana pellet. This board is located in a box whose top can be opened or closed. The task can consequently be performed unimanually with or without visual feedback. Experiments were conducted on 6 adult macaque monkeys. When the animals reached a behavioural plateau in manual dexterity tests, they were subjected to a permanent unilateral cortical lesion performed in the hand representation of M1. After the lesion, the monkeys were included either in a control group, or in an adult neural progenitor cell therapy protocol or treated with anti-Nogo-A antibody. The Brinkman box test was pursued after the lesion, with and without visual feedback. We present preliminary data for the contralesional and ipsilesional hands about the contact time, the time intervals between successive wells/pellets, the precision grip shaping time, prehension strategies and different types of errors. These parameters are differentially relevant according to the monkeys. Post-lesion somatosensory-related deficits similar to a sensory agnosia were among others observed.

## J19 Functional reorganization of the medial temporal lobe memory system following neonatal hippocampal damage in monkeys

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In humans, the hippocampus is essential for the processing of semantic and episodic memories, and damage to this structure in adulthood results in amnesia. In contrast, semantic memory is largely preserved in subjects who sustained hippocampal damage early in life, suggesting that the medial temporal lobe memory system might undergo structural and functional reorganization after neonatal hippocampal lesion. Similarly, we have previously shown that spatial relational learning is impaired in monkeys who sustained hippocampal lesion during adulthood, whereas spatial relational learning persists in monkeys who sustained hippocampal lesion shortly after birth. Here, we aimed to characterize the structural and functional reorganization of the medial temporal lobe memory system in macaque monkeys (Macaca mulatta) following neonatal hippocampal lesion. Shortly before death, animals explored a novel open-field environment in order to activate brain structures involved in spatial learning and memory. Quantitative analyses of expression of the immediate-early gene c-fos, a marker of neuronal activation, were performed to determine the brain structures that might enable spatial relational learning following early hippocampal lesions. Preliminary findings suggest that the perirhinal and entorhinal cortices are overall less activated by spatial learning in monkeys following early hippocampal lesions, as compared with control monkeys. Interestingly, decreased neuronal activation might be particularly important in the caudal entorhinal cortex, which is normally involved in spatial memory processing. In contrast, neuronal activation might be higher in the cingulate and retrosplenial cortices, which project to the medial temporal lobe and are also known to contribute to spatial memory processes in normal monkeys. These results suggest that the functional reorganization of a large brain network might contribute to the preservation of memory function following early hippocampal damage.

## J20 Investigating the dynamics of epileptic networks in a mouse model of temporal lobe epilepsy

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Epilepsy is one of the most frequent neurological disorders and is typically divided into focal and primary generalized types. In focal epilepsies, a localized brain area, also named seizure-onset zone, accounts for the generation of ictal and possibly interictal events. Yet, strong evidences suggest that even the development of focal epileptic activity is dependent on the establishment of an epileptic network that involves areas remote from the localized focus. Moreover, it is highly suspected that the epileptic focus is not independent within brain networks, ie. the focus affects large-scale brain networks and modify their activity even if they are not disturbed by the initial injury. Here, we study the epileptic activity in awake mice that were previously injected unilaterally in the hippocampus with kainate. To record the brain activity, we use 32 electrodes distributed equally over both hemispheres. Prior to injection, mice were recorded several times to acquire their baseline EEG activity: we could identify the background activity and typical graphoelements. These components of the spontaneous “pre-injected” brain were compared to post-injection spontaneous brain activity. We then analyzed the EEGs in epileptic mice and noted two features not present prior to injection: focal and diffuse spikes. Focal spikes are typically detected by 1 to 3 electrodes, whereas diffuse spikes involve several different electrodes and are followed by a flattening of the EEG. These were present in all mice after injection. The network recruited by the interictal activity appears to be reproducible between and within animals and

mainly involves electrodes over the contralateral hippocampus and frontal regions a few milliseconds after the spike. We are currently studying the evolution through time of these different epileptic features. This is the first large-scale brain network recording of epileptic activity in awake mice. We plan to study the intracortical activity in the two identified target regions of the epileptic focus. A better knowledge of the development and evolution of epileptic networks will surely help to develop tools aimed to control, modify and ultimately treat these dysfunctional networks.

## J21 Involvement of the receptor for advanced glycation end-product (RAGE) in redox dysregulation and neuroinflammation in an animal model of schizophrenia

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Schizophrenia is a major psychiatric disease which involves both genetic and environmental factors. Glutathione (GSH), an important cellular antioxidant and redox regulator, is decreased in CSF and brain of patients. The key GSH synthesizing genes present polymorphisms associated with the disease. Thus, a redox dysregulation during neurodevelopment is a critical risk factor for schizophrenia, on which converge genetic impairments of glutathione synthesis and environmental vulnerability factors generating oxidative stress.
Increasing evidence also points to immune dysregulation in schizophrenia. Anomalies in peripheral immune cells as well as dysregulation of immune-related genes have been reported in schizophrenia brain. However the causes and the underlying mechanisms of this subclinical, inflammatory-like state are still unclear. As oxidative stress is known to induce inflammatory processes, the latter were studied in a transgenic animal model with GSH deficit (GCLM-/-). RAGE represents one potential link between oxidative stress and inflammatory process, as it is activated by ROS and induces inflammatory gene expression. We compared by immunohistochemistry the expression of RAGE and microglia activation markers in the anterior cingulate cortex between GCLM-/- and WT mice at P40 and at P90 following oxidative stress induction by a dopamine uptake blocker between P30 and P40 or between P80 and P90. At both time-points, the number of Iba1-immunoreactive (IR), CD11b-IR and CD68-IR cells were increased in GCLM-/- compared to WT at basal level with no further increase after an additional oxidative stress, suggesting a pro-inflammatory state. RAGE was shown to be expressed in the cytoplasm of neurons in both genotypes. At P40, RAGE-IR cells number was increased in GCLM-/- while it was decreased following oxidative stress induction compared with WT at basal level. However, at P90, RAGE-IR was decreased in GCLM-/- compared to WT. In addition, S100b, a ligand of RAGE, was differentially regulated in GCLM-/- mice compared with WT mice. These inflammatory process anomalies occurring during brain early development may induce structural and morphological impairments related to schizophrenia.

## J22 Adaptation to Incomitant Vergence Disparity

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Purpose

Vergence movements are slow disconjugate eye movements which may be triggered by image disparity or accommodation. There exist numerous clinical contexts where image disparity may vary with the direction of gaze. A common example is a sixth cranial nerve palsy with increasing image disparity in gaze toward the affected muscle. Adaptive changes to such incomitant image disparity have been poorly

investigated and are the scope of this study.

Methods

Vergence stimuli of gaze dependent magnitude were used to mimic the image disparity of an incomitant strabismus. In a first experiment prisms were placed such that stimuli were viewed through the prisms in one gaze direction but not in the other gaze directions. In a second experiment we used a haploscope to modify image disparity according to gaze. We measured vergence responses that were made after a saccade shifting gaze from left to right, with increased image disparity in right gaze. We analysed changes of rise time or mean velocity, latency, and amplitude over time.

Results

Increased image disparity in right gaze led to a decrease of vergence rise time and latency within minutes. Using the haploscope to deliver vergence stimuli, we again found a significant increase in vergence kinetics (mean velocity), but not in latency.

Conclusion

In this study we show that repetitive increase of the vergence demand leads to rapid improvement of the vergence response kinetics with a moderate effect on the latency. This type of vergence plasticity helps to rapidly restore stereovision after a saccade is made into a field of gaze with increased image disparity.

## J23 Differential effect of FAD-APP and g-secretase modulators of APP processing

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Mutations in the amyloid precursor protein (APP) and various chemical -secretase modulators affect the processing of APP by the -secretase complex and the production of the Alzheimer's disease associated amyloid-beta peptide A42. Here we demonstrate that pathological amino-acid substitutions in the transmembrane domain of APP causing aggressive early-onset familial Alzheimer's disease affect both - and - cleavage sites, by raising the A42/40 ratio and inhibiting the production of AICD50-99, one of the two physiological APP intracellular domains (ICDs). This is in sharp contrast to -secretase modulators, which shift the toxic A42 production towards the shorter A38, but unequivocally spare the -site and APP- and Notch-ICDs production. Molecular simulations suggest that familial Alzheimer's disease mutations modulate the flexibility of the APP transmembrane domain and the presentation of its -site, modifying at the same time, the solvation of the -site.

## K. Clinical Neuroscience

### K1 Severity of neglect may increase with motion - insights from a touchscreen-based cancellation task

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Background and Purpose: In stroke patients, diagnosis of neglect is often made by paper-pencil cancellation tasks. These tasks entail static stimuli, and provide no information concerning possible changes in the severity of neglect symptoms when patients are confronted with motion. The identification of specific clinical characteristics, alerting clinicians about a possible worsening of neglect symptoms in the presence of motion, would thus be desirable.

Methods: Twenty-five patients with left spatial neglect after right-hemispheric stroke were tested with a new touchscreen-based cancellation task. This task allows to directly contrast the cancellation behaviour under a static (targets are static) and a dynamic (targets move on a random path) condition. Since visual field deficits are often found after a brain lesion, the integrity of the optic radiation was considered as an additional factor.

Results: In patients with major damage to the optic radiation, the severity of neglect significantly increased in the dynamic condition. In patients with minor damage to the optic radiation, no difference in the cancellation behaviour between the static and dynamic conditions was found.

Conclusion: In stroke patients with neglect, it is important to specifically assess whether a damage of the optic radiation is also present, since these patients may show a deterioration of their neglect symptoms in daily life when confronted with motion.

### K2 Visual exploration of co-speech gestures in aphasic patients: An eye-tracking study

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Introduction

Gesturing, which includes co-speech gestures, is a crucial part of human communication. Healthy participants spend about 88-95% of the time fixating a speaker's face, while only a minority of fixations is directed at gestures (Beattie et al., 2010; Gullberg & Holmqvist, 1999). However, it is unclear whether aphasic patients display similar patterns. The present study aimed to investigate the visual exploration of co-speech gestures in aphasic patients.

Subjects and Methods

20 aphasic patients and 20 controls participated in this study.

75 short video sequences in three experimental conditions that varied in the level of congruity between speech and gestures were

created. After each sequence, participants had to judge this congruity by keypress. A remote eye-tracking device allowed comfortable gaze tracking and off-line analysis of parameters such as fixation duration on predefined areas of interest (AOIs).

Results

Repeated measures ANOVAs were performed for cumulative fixation duration (the total time a specific AOI was fixated). This yielded a significant interaction between the factors AOI * Group, indicating that aphasic patients spent more time fixating the hands compared to healthy controls, while healthy controls fixated more on the speaker's face compared to the patients.

Discussion

In line with previous research (e.g. Gullberg & Holmqvist, 1999), all participants spent most time fixating the speaker's face. Aphasic patients showed an altered visual exploration behavior insofar as they looked less on the face but more on the gesturing hands compared to controls. Aphasic patients might thus rely more on the additional (nonverbal) information presented by gestures in order to understand verbal utterances and to judge increasingly complex sequences. It could also be assumed that the visual attention of aphasic patients is more strongly influenced by bottom-up information processing, such as gestural movements that attract attention unconsciously.

## K3 Perception of co-speech gestures during dyadic conversations: Evidence for altered gaze patterns in aphasic patients

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Background: Aphasia is an acquired language disorder that occurs commonly after left-hemispheric brain damage. Since patients suffering from aphasia are restricted in their verbal abilities, they may compensate their verbal deficits by using gestures. Previous studies have shown that some patients could use gestures as compensatory strategies, while others did not. In contrast to previous research which focused mainly on gesture production, the present study investigated the perception of co-speech gestures in aphasic patients. We expected that aphasia influences gaze behavior in patients and that altered gaze patterns would be associated with content-related comprehension.

Methods: 20 aphasic patients and 20 healthy control subjects matched for age, sex, and education were included in the study. Gaze data was collected by means of a contact-free infra-red eye tracker while subjects were watching videos of dyadic conversations. For data analysis, a region of interest (ROI) analysis was conducted.

Results: In line with previous findings, we found that subjects rather gazed at the face of the speaking interlocutor than at the gesturing hand. Most interestingly, we found main effects of gesture, group and a ROI x group interaction. Subjects tended to look less at the face and fixated more on the actor's hands during the presence of a co-speech gesture. Overall, aphasic patients gazed less at the face region and tended to look more on the hands compared to healthy controls. Further, we found a trend for an association between the time spent looking at the face and content-related comprehension.

Conclusion: The face is the main attractor for somebody who is following a dyadic conversation. However, the presence of co- speech gestures seems to elicit a partial shift of the attention to the gesturing hand. As expected, we could show that aphasic patients display altered gaze patterns. They tended to fixate less on the face, a finding that might be related to language comprehension.

## K4 Transcriptome analysis of sleep deprivation associated neuroprotection in a rodent model of stroke

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Sleep-wake disturbances are frequent after stroke and they are linked with poorer rehabilitation and long-term outcome. However if sleep deprivation (SD) is performed before stroke, induces ischemic tolerance as observed in other forms of preconditioning. The mechanisms underlying this neuroprotective effect are not well understood and probably involve multiple molecular pathways. The main aim of this study was to identify which genes are involved in the neuroprotective mechanisms elicited by SD preconditioning through the use DNA oligonucleotide microarrays.
A microarray study of gene expression was performed at 3 days after pre-stroke SD in adult Sprague-Dawley rats (n = 16). Animals were assigned to four experimental groups: 1) TSD.Is: total SD performed before stroke; 2) nSD.Is: stroke performed without previous SD; 3) TSD.Sham: TSD performed before sham surgery ; 4) Sham: sham surgery without SD. SD was performed during the last 6h of the light period by gentle handling and ischemia was induced immediately after.
Stroke induced an upregulation of gene expression (74% of total modified genes) in the ischemic hemisphere compared to Sham animals. SD resulted instead in a pronounced gene downregulation (84% of total modified genes). Compared to nSD.Is, TSD.Is animals showed transcriptional changes in genes involved in cell cycle checkpoint regulation and immune response. Moreover an upregulation of genes involved in the neuroendocrine pathway was also observed. This pathway have never been described for other forms of preconditioning and includes: melanin concentrating hormone (MCH) glycoprotein hormones-- polypeptide (CGA), hypocretin (HCRT), observed in TSD.Is animals compared to nSD.Is

These data suggest that SD preconditioning induces gene expression changes similar to what observed with hibernation preconditioning which lead to a cellular arrest and an inhibition of the inflammatory response. The inactivation or temporary arrest of these mechanism reduce the release of several cytotoxic agents that could aggravate the neuronal damage. Moreover we have observed an upregulation of a neuroendocrine pathway that could mediate neuroprotection by the modulation of estradiol levels, a hormone which is already known for its protective effect in cerebral ischemia.

## K5 An fMRI-Study on context-specificity of inhibitory functions in alcohol-dependency: Preliminary results

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Introduction: Alcohol-dependency is a common disease with many negative consequences in the daily life. A typical symptom of alcoholic-patients is the persistent and uncontrollable desire to consume alcohol. Inspite of different treatments, alcohol- dependency has a relapse rate of about 85%. This high rate is facilitated by a dysfunction of cognitive control-processes. In order to understand this disease sustaining factor, the present study investigated the neurophysiological correlates of inhibition of alcoholic-patients in a neutral as well as an alcohol-related context.
Methods: A total of 18 participants (9 alcohol-dependent patients and 9 healthy controls) were recruited and event-related functional magnetic resonance imaging was used to assess the neurophysiological correlates of inhibition in an alcohol-related as well as neutral context. Therefore, pictures of alcohol as well as neutral contexts were presented and the participants had to press a button for every picture, except if the same picture appeared twice in a row. These neurophysiological correlates of context-specific inhibition-abilities were compared in both groups.

Results: When comparing correct stop-trials in alcohol-related to neutral context, only alcohol-dependent patients showed significant hyperactivation in frontal regions (superior and medial gyrus frontalis, anterior gyrus cinguli, gyrus paracentralis and the gyrus praecentralis). No significant differences were found in any of the behavioral analyses.
Discussion: These preliminary results thus indicate that successful inhibition in a drug-related context demands additional resources in patients. Especially the hyperactivation of the anterior gyrus cinguli might be important because of its involvement in decision-processes. In the absent of deficits in behavioral data, this suggests that alcohol-dependent patients need more neuronal activity to achieve the same performance-level like healthy controls.

## K6 Feasibility of neurofeedback training to modify brain states relevant for mental health.

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Spontaneous EEG signal can be parsed into sub-second time epochs with quasi-stable EEG scalp field topographies separated by rapid configuration changes. These epochs are called microstates and manifest different brain functional states exerting different effects on information processing. Resting-state EEG microstates in patients with schizophrenia show concise and well replicable peculiarities: In several independent samples, a specific class of microstate with a fronto-central distribution has been found to be consistently shorter in schizophrenic patients when compared to healthy controls, the so called microstate class D. This shortening has been correlated to positive psychotic symptoms. Therefore it is reasonable to think that if patients can learn to normalize microstate class D; this might help reducing psychotic symptoms. A useful method for learning to self-regulate brain states is EEG based neurofeedback. This method is effective, inexpensive and has been used for research and treatment like in epilepsy, ADHD, stroke and others. The present study aims to explore if healthy subjects are able to regulate the presence of class D microstates by means of neurofeedback training. We present the technical setup and the training protocol, which includes baseline assessments, training and transfer trials. Preliminary results suggest that up-regulation of microstate Class D is feasible in a healthy population.
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## K7 How theta amplitude is related to fMRI resting state networks during working memory in patients with schizophrenia

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Deficits in working memory processes are a core feature of schizophrenia. While in healthy subjects, the fMRI-BOLD signal is usually decreased in regions of to the so called default mode network (DMN) during tasks, patients seem to both fail to deactivate these task-negative regions as well as to activate task positive regions. Furthermore, working memory load induces an increase in frontal EEG theta (5 - 8 Hz) power in healthy subjects, while reduced activity has been found in this patient group. The simultaneous measurement of EEG and fMRI has become an established technique in order to obtain spatially well- defined indices of metabolic activity from the fMRI as well as EEG based information about the fast dynamics of stimulus processing. With the so called covariance mapping, the fluctuations of fMRI resting state networks (RSN) are temporally correlated with the dynamics of EEG spectral amplitudes. As a result, the spatial distributions of frequency domain EEG fluctuations that were significantly associated with the dynamics of the RSNs are obtained. We will present preliminary results of computed covariance maps of EEG theta amplitude from the retention period of a verbal Sternberg

working memory task and the dynamics of the DMN and a fronto-parietal control network (FPCN) in a preliminary single-trial analysis on schizophrenia patients and healthy controls.

## K8 Improving robustness of brain GABA measurements in human brain

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MR Spectroscopy (MRS) is the only method to measure GABA levels in the human brain non-invasively. However, accuracy, precision and spatial resolution are all limited, given the low SNR of the technique. Hence, improvements in terms of sensitivity and clinical robustness are needed. The most common method to measure GABA on clinical MR scanners is MEGA editing [1] based on alternating selective refocusing of a specific J-coupling. Ideally, this scheme separates the satellite lines of the GABA triplet signal at 3 ppm from overlapping signals. In brain, it was found that with the basic sequence macromolecule (MM) signals co-edit with the GABA signal, which can be prevented if the control pulse is placed symmetrically to the MM coupling partner at 1.7 ppm. In addition, the add/subtract scheme is susceptible to small experimental instabilities that may lead to frequency shifts and amplitude changes, as well as instable water suppression, which may all result in suboptimal cancellation of untargeted signals and an unknown signal shape for the GABA multiplet. In this study, we have combined MEGA PRESS editing with the metabolite cycling technique suggested for non-water suppressed MR spectroscopy [2]. The method, as tested in vitro and on 6 subjects, provided excellent water signal elimination while retaining a water-only spectrum that can be used for frequency, phase and lineshape reference, as well as a continuous quantification standard. Post- acquisition frequency realignment is much easier than when using the low SNR metabolite signals. Even with rather severe frequency drifts, it was possible to reconstruct meaningful difference spectra – though they will have to be fitted using the knowledge of overall broadening from the water peak. With optimized parameters, it was found that co-editing of MMs could be prevented without large penalty in GABA signal loss.

1. Mescher M et al. NMR Biomed 11:266.
2. MacMillan EL et al. Magn Reson Med 65:1239.

## K9 Neural correlates and predictive value of auditory discrimination in early coma and hypothermia

**Authors**

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Auditory discrimination, assessed by mismatch negativity (MMN) paradigms has been recently studied in acute coma in patients treated with therapeutic hypothermia (TH), showing that the progression of auditory discrimination over the first two days of coma is informative of the patient's chances of awakening. Even though TH is increasingly applied as an acute coma treatment, neural functions under TH still remain under-explored. Here, we expanded previous work on 30 patients to a cohort of 58 patients in total, in order to evaluate the suitability of this approach for use in a clinical routine and to systematically study the neural correlates of auditory discrimination under hypothermia and early coma. We recorded electroencephalography (EEG) responses during a MMN paradigm under TH and after re-warming to normal temperature (NT). Single-patient topographic EEG activity was analyzed by decoding responses to standard vs. deviant sounds. Average decoding performance for 34 patients who later awoke was 0.63±0.01 in TH and 0.63±0.01 in NT, and for 24 patients

who later died 0.66±0.01 and 0.62±0.01 (TH/NT). Decoding performance improved from TH to NT for 19 patients; out of them 18 awoke beyond a vegetative state within three months (0.95 predictive power; 95% CI: 0.74-1.00). Additional analyses in a sub-group of 22 patients showed that 7 out of 22 had above chance results in decoding responses to standard vs. duration deviant sounds (Wilcoxon signed- rank test, $p<0.01$) in TH (3 awoke) and 6 in NT (5 awoke). The time-periods of differential responses appeared consistently in TH at ~370ms and in NT at ~135ms and ~280ms post-stimulus onset. These later latencies observed during TH are consistent with the idea that TH might down-regulate cerebral metabolism and slow down neural activity. Moreover, the prediction results on 58 patients encourage the use of this approach in a clinical environment and promise to provide an automatic and reliable way for predicting awakening.

## K10 Visual symptoms in Parkinson's disease

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Background: Visual symptoms are common in Parkinson's disease (PD). The remain under-diagnosed but can contribute to patient and caregiver distress. The detection of visual symptoms is important for differential diagnosis and patient management.

Aim: To establish the prevalence of recurrent visual complaints (RVC) and recurrent visual hallucinations (RVH) and to investigate their interaction in PD patients and controls.

Methods: This cross-sectional study included 88 PD patients and 90 controls. RVC and RVH were assessed with a visual symptom questionnaire and the North-East-Visual-Hallucinations-Interview (NEVHI).

Results: Double vision (PD vs. Controls: 18.2% vs. 1.3%; $p < 0.001$), misjudging objects when walking (PD vs. Controls: 12.5% vs. 1.3%; $p < 0.01$), words moving whilst reading (PD vs. Controls: 17.0% vs. 1.3%; $p < 0.001$) and freezing in narrow spaces (PD vs. Controls: 30.7% vs. 0%; $p < 0.001$) were almost exclusively found in PD patients. The same was true for recurrent complex visual hallucinations and illusions (PD vs. Controls: both 17.0% vs. 0%; $p < 0.001$). Multiple RVC (43.2% vs. 15.8 %) and multiple RVH (29.5% vs. 5.6%) were also more common in PD patients (both $p < 0.001$). RVC did not predict recurrent complex visual hallucinations; but double vision ($p = 0.018$, $R2 = 0.302$) and misjudging objects ($p = 0.002$, $R2 = 0.302$) predicted passage hallucinations. Misjudging objects also predicted the feeling of presence ($p = 0.010$, $R2 = 0.321$).

Conclusions: Multiple and recurrent visual symptoms are common in PD. RVC predicts the minor forms of hallucinations, but not recurrent complex visual hallucinations.

## K11 Deviant dynamics of EEG resting state pattern in 22q11.2 deletion syndrome adolescents: a vulnerability marker of schizophrenia?

**Authors**

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Previous studies have repeatedly found altered temporal characteristics of EEG microstates in schizophrenia. The aim of the present study was to investigate whether adolescents affected by the 22q11.2 deletion syndrome (22q11DS), known to have a 30 fold increased risk to develop schizophrenia, already show deviant EEG microstates. If this is the case, temporal alterations of EEG microstates in 22q11DS individuals could be considered as potential biomarkers for schizophrenia. We used high- density (204 channel) EEG to explore between-group microstate differences in 30 adolescents with 22q11DS and 28 age- matched controls. We found increased presence of one microstate class (class C) in the 22q11DS adolescents with respect to controls that was associated with positive prodromal symptoms (hallucinations). A previous across-age study showed that the class C microstate was more present during adolescence and a combined EEG-fMRI study associated the class C microstate with the salience resting state network, a network known to be dysfunctional in schizophrenia. Therefore, the increased class C microstates could be indexing the increased risk of 22q11DS individuals to develop schizophrenia if confirmed by longitudinal studies.

## K12 Impaired slow wave sleep downscaling in West syndrome – a malignant epilepsy of infancy

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West syndrome is a severe epileptic encephalopathy of infancy, characterized by infantile spasms, risk of retardation, and an abnormal electroencephalogram (EEG) pattern known as hypsarrhythmia, which can be treated with corticosteroids. Hypsarrhythmia is characterized by a random, high voltage activity pattern and is more frequently seen during non-rapid-eye movement (NREM) sleep. The restorative function of NREM sleep has been linked to downscaling, a neuronal process ensuring a balance of global synaptic strength, which is important for normal cortical functioning and development. A key electrophysiological marker for this downscaling is the reduction of the slope of EEG slow waves across the night. We compared overnight changes in the slope of slow waves between 14 untreated West syndrome patients (6.0 ± 0.6 months) and healthy age and gender matched controls. Patients were tested again during two follow-up nap recordings during and after treatment with corticosteroids. West syndrome patients showed a diminished overnight reduction in the slope of slow waves compared to controls ($p=0.009$). Moreover, untreated patients revealed overall steeper slope slow waves. During corticosteroid treatment the slope of slow waves was reduced in patients compared to controls ($p=0.001$). After successful treatment the slope of slow waves was similar between patients and controls. Our results provide evidence for reduced downscaling in West syndrome. This altered sleep dependent regulation of synaptic strength in West syndrome may contribute the underlying patho-mechanism of the developmental regression. Moreover, the marked reduction in the slope of slow waves during corticosteroid treatment may reflect a loss of synaptic connections due to elevated glucocorticoid level and thus may provide a potential mechanistic explanation for this treatment strategy.

## K13 Electrophysiological Monitoring of Residual Hearing During and After Cochlear Implantation

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Background
Improvement of surgical techniques and electrode design increased hearing preservation rates after cochlear implantation in recent years. However, in a considerable amount of patients partial or complete loss of residual hearing still occurs. The underlying mechanisms are poorly understood so far. Among many others acute direct trauma from electrode insertion and hydraulic forces as well as delayed events such as foreign body reaction and molecular activation leading to delayed neural injury are discussed. Our goal was to further assess time and mechanisms of loss of residual hearing after cochlear implantation and see if changes in electrocochleographic hair cell and neural responses correlate with postsurgical psychoacoustic test findings.
Methods
Patient with some degree of residual hearing undergoing cochlear implantation were included. Electrocochleographic measurements were conducted by a monopolar measurement electrode placed next to the round window before opening the cochlea and immediately after cochlear implantation. In some patients further measurements with different electrodes of the cochlear implant itself as measurement electrode followed in growing intervals in the first few days and weeks after surgery. At each session cochlear microphonic (CM), summating potential (SP), compound action potential (CAP), and auditory nerve neurophonic (ANN) responses to tone bursts of different intensities at frequencies of 250 to 2000Hz were recorded. Additionally, pre- and postsurgical psychoacoustic tests including pure tone audiometry and speech perception tests were performed.
Results
Even in patients with very limited residual hearing in presurgical pure tone audiometry hair cell and neural responses were measurable by electrocochleography. Immediately after surgery hair cell and neural responses were still detectable in most patients. These findings correlated not with partial or complete loss of residual hearing in pure tone audiometry after 4 weeks.
Conclusion
Electrocochleography allows the assessment of cochlear and neural status during and after cochlear implantation. Immediately after surgery loss of electrocochleographic responses occurs rarely. This suggests that with current surgical techniques and electrode designs in most cases loss of residual hearing is not due to acute trauma during surgery. More likely changes within the first weeks are causing hair cell or neural injury. Further assessment of these mechanisms is possible by repeated electrocochleographic measurements with the electrodes of the cochlea implant itself.

## K14 Development and evaluation of a new instrument to measure higher visual functions

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Visual perception can be defined as the integration of a series of cognitive processes, including reception, organization and elaboration of the visual information sent to the cerebral cortex. Higher visual functions (HVF) are mainly involved in such processes and are of key importance in everyday life activities. People with impaired HVF complain about difficulties such as noticing persons or relevant objects, avoiding obstacles, driving, walking and many other activities. Since the information coming from the left visual hemifield and the right one is elaborated into the right brain hemilobe and the left one, respectively, people with unilateral brain lesions may perceive the visual world differently depending on the lesion. Currently there are no methods to quantify these differences and, thus, the significance of the

brain lesions. In this project, a new computer-based test (HVF test battery) to measure HVF has been developed and will be integrated into an existing perimeter device (Octopus 900 – Haag Streit, Köniz). This new computer-based clinical test follows a balance paradigm, where people fixate at a marker point straight ahead in front of them while watching two images (reference and image under manipulation) projected the right and left visual hemifield. The task is to adjust the feature of the image under direct manipulation until it is perceived as similar as possible to the reference image. The presented images consist of circles and ellipses for testing shape recognition, rotating lines for perception of orientation, and moving dots for motion and speed perception. The degree of the final differences between the two images is an indicator of the significance of the impairment: higher the difference, higher the degree of the impairment. In classical neurological tests, the degree of impairment is judged by the final score which is usually the number of items correctly recognized. The HVF test battery collects quantitative data that correspond to the degree of the impairment. So far, forty-seven healthy young subjects (mean age = 30.87, standard deviation = 5.65) have been tested in a pilot study and a satisfaction questionnaire has been used as a system usability score of the battery. The results indicated that people with intact higher visual functions are able to discriminate small differences in shape, size, orientation, speed and direction of motion with an accuracy of (0.18 ± 0.15)°, (0.17 ± 0.10)°, (2.56 ± 1.57)°, (0.22 ± 0.16)°/s and (9.67 ± 7.70)°, respectively. Furthermore the participants liked the HVF test battery more than the existing standard tests. Furthermore, the motivation and the self- estimation of the performances also resulted higher for the HVF tests. In the next step, it is planned to compare the performances of patients with unilateral brain lesion in the region of the visual pathway with age-matched healthy controls.

## K15 Prognostic and diagnostic value of quantitative EEG in comatose patients

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Aims: EEG is essential for diagnostic and prognostic assessment of patients on intensive care units (ICU). The aim of this study was to assess the diagnostic and predictive value of quantitative analysis of EEG signals (qEEG) in comatose patients.
Methods: Consecutive comatose patients (aged >16 years; GCS < 8) who had an EEG between January 2008 and January 2012 in the ICU of the University Hospital Bern were included in this retrospective study. Exclusion criteria were: brain hemorrhages, traumatic head injury or a recent history of brain surgery, or qualitatively insufficient EEG. In case of multiple examinations, only the first EEG was analyzed. Patients were classified according to clinical outcome (alive or deceased at discharge from the ICU), and according to etiology of coma (hypoxic vs. non-hypoxic; the non-hypoxic group was then further divided between infectious, metabolic/drug-drug-related, and epileptic causes for coma). The decision to continue or limit ICU treatment of the patients was not dependent on quantitative EEG analysis. We considered bipolar derivations corresponding to anterior (F3-F4), posterior (P3-P4), left (F3-P4) or right (F4-P4) brain regions. Four qEEG methods were uses between these bipolar derivations in the antero-posterior (intra-hemispheric) or left-right (inter-hemispheric) axis: relative delta power (RDP) asymmetry, zero-lag cross-correlation (CC), symbolic mutual information (sMI) and symbolic transfer entropy directionality (sTE). Differences between patient groups with respect to qEEG were examined with Wilcoxon rank-sum test or 1-way ANOVA. The prediction value of the four qEEG methods was assessed with a Bayes Classifier, based on mixture of Gaussians
Results: RDP: A higher anterior-posterior asymmetry index was found in the group of patients with bad outcome ($p< 0.0001$). The index was also larger in patients with hypoxia as in those with epileptic cause of coma. CC: The inter-hemispheric synchronization was significantly higher in patients with bad outcome ($p< 0.0001$); interestingly, the intra-hemispheric synchronization was higher in case of good outcome ($p<0.05$). sMI: no significant difference were observed between groups. sTE: an information flow predominantly from anterior to posterior was associated with a favorable outcome ($p<0.05$) Classifier: The most significant features for predicting clinical outcome with a Bayes classifier were the anterior-posterior asymmetry index of MI and RDP (maximum accuracy was 84%). Adding clinical

information such as motor response to pain, or pupillary reflex did not improve the prognostic accuracy.

Conclusion: quantitative analysis of early EEG can contribute to the prognostic assessment of comatose patients.

## K16 Feasibility of peak cardiovascular exercise testing using a robotics-assisted tilt table in dependent-ambulatory stroke patients

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Background: Cardiopulmonary fitness is compromised in stroke patients. Previous studies included independent walkers with sufficient motor power to perform exercise testing on a treadmill or a cycle ergometer. There are limited data on cardiopulmonary fitness in non-ambulatory stroke patients unable to test with standard devices. We utilised a robotics-assisted tilt table (RATT - Erigo, Hocoma AG, Switzerland) augmented with force sensors in the thigh cuffs, a work rate estimation algorithm and a real-time visual feedback system to guide the patient's exercise work rate. The present study evaluated the feasibility of the RATT with volitional feedback control of work rate for peak cardiopulmonary performance testing in dependent- ambulatory stroke patients.

Methods: Post-stroke subjects had functional ambulatory category 3 and no contraindications for exercise testing. Patients performed 3 separate exercise tests: a familiarization, an incremental exercise test (IET) and a constant load test; only the IET results are reported here. Outcome measures for the IET were peak oxygen uptake (VO2peak), peak heart rate (HRpeak), respiratory exchange ratio at VO2peak (RERpeak), and the Borg CR10 scale for dyspnea and leg effort.

Results: Four stroke patients (55±3.9 years [mean ± sd], 2 males and 2 females) were included. VO2peak, RERpeak and HRpeak were 12.3±3.6 ml/kg/min, 1.05±0.1 and 122.3±3.5 beats/minute, respectively. Maximal work rate was 25.1±9.9 W. These are considered to be substantial responses in these severely-compromised neurological patients: mean HRmax was 74% of the age-predicted maximum and mean VO2peak was 46% of the predicted peak for normal subjects. Mean dyspnea and leg effort were 6.8 and 7.2 (Borg CR10 scale), respectively.

Conclusions: The RATT with volitional work rate control elicits substantial cardiopulmonary responses and is deemed feasible for peak cardiopulmonary performance testing in dependent-ambulatory stroke patients.

## K17 Functional ictal networks in patients with pharmacoresistant epilepsy

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In this retrospective study we used symbolic transfer entropy (STE) to characterize functional ictal network derived from intra- cranial EEG recording in 13 patients with pharmaco-resistant epilepsy. STE is a non-linear and model free information theoretic for quantifying magnitude and direction of information flow between signals. For each seizure we identified “hub” electrodes, namely electrodes with maximal incoming, outgoing and total (bidirectional) information flow. The localisation of these hub electrodes were correlated with clinical outcome after epilepsy surgery. We found that a higher percentage of electrode with maximal outgoing (p=0.04) or total information flow (p=0.12; when considering electrode at border of the resected area: p=0.06) were predictor of good clinical outcome.

Furthermore, we found that the maximum of information transfer often occur in the middle of the seizure, with a second local maximum before seizure termination. Our work shows that quantitative EEG methods can contribute to identify brain area crucial for seizure development, and which could be targeted by invasive therapeutical procedures (epilepsy surgery or stimulation).

## K18 The heart in the head: EEG-fMRI pulse artifact detection and correction using high density EEG topography

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Simultaneous EEG-fMRI recordings allow investigating physiological and pathological brain networks. The Pulse Artifact (PA) is mainly due to the motion of electrodes and wires in the magnetic field occuring after each heart beat. PA depends on the orientation of the resulting loops respect to the magnetic field. It needs to be corrected to allow reliable EEG interpretation and processing but its correction based on electrocardiogram (ECG) an be difficult. In this study we propose a novel method to improve the detection of PA considering its voltage topography. We acquired high density EEG-fMRI (256 electrodes) with simultaneous ECG at 3T on 4 alive phantoms, 5 healthy subjects and 2 epileptic patients. For 3 of the phantoms we recorded also 5 minutes inside the scanner without MRI sequence. We selected a subset of electrodes on facial and temporal part of the head where the PA is prominent with a clear asymmetric topography to estimate the artifact as a difference between right and left. Peaks were detected on the estimated PA or ECG. The accuracy of the detection was assessed with the following criteria: (i) standard deviation, (ii) kurtosis and (iii) confinement in the physiological range of the inter-peaks intervals. The detection of the peaks was significantly better with the PA estimation in 4/5 healthy, in both the patients and in ¾ recording on alive phantoms during the sequence. This new method will improve the detection of epileptic patterns and the study of haemodynamic correlates of normal and abnormal neural activity.

## K19 An electrophysiological investigation of emotional change: preliminary results

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Many psychotherapy researchers agree that emotional change is critical to therapeutic progress. In emotion-focused and Gestalt therapy, one technique to foster emotional change is the empty chair dialogue. Psychotherapy research has yielded ample evidence that this technique helps to alleviate longstanding interpersonal grievances (‘unfinished business’) and facilitates emotional change. Until now, little is known about the neurophysiological correlates of such emotional change. The present study thus aims at adding a further level of analysis to psychotherapy research, and may enrich knowledge about mechanisms of change. Neurophysiological correlates of emotional change were investigated using multi-channel electroencephalography. Individuals experiencing ‘unfinished business’ were guided by experienced therapists to participate in an empty chair dialogue. Event- related brain potentials were recorded before and after the intervention while participants were viewing pictures of the person central to their interpersonal grievance as well as pictures of control persons. Event related potentials are compared regarding topography and overall signal strength. Preliminary results will be discussed regarding neurophysiological mechanisms of action potentially occurring during emotional change.

## K20 Narcolepsy-Cataplexy and its awareness in Switzerland

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Introduction: Narcolepsy is a rare sleep-wake disorder, with an estimated prevalence of 10 to 50 patients among 100,000 people. Narcolepsy patients complain about excessive daytime sleepiness, loss of muscle tone caused by an emotional trigger (cataplexy), hypnagogic/hypnopompic hallucinations, sleep paralysis and – paradoxically - disturbed night sleep, inducing severe social problems.
Methods: We investigated the quality of life of narcoleptic patients in Switzerland as well as its awareness in the public. In a first survey 30 narcolepsy patients who are members of the SNaG, filled out the "Bern questionnaire" and a specifically designed questionnaire focusing on psycho-social integration. In a second survey 80 students and teachers of the Lugano high school (Liceo Lugano 1) filled out a questionnaire about their knowledge on narcolepsy-cataplexy.
Results: As expected sleepiness was reported by 23 of 27 responders and weakness with laughter (cataplexy) by 15 of 25 responders. Also fatigue was reported by 17 of 26, but physical fatigue was reported by 11 of 26 and increased sleepiness during physical activity only in 5 of 24. Accidents due to sleepiness were reported by 9 of 26 patients, but only once while driving. Nineteen of 30 participants were driving regularly and only 3 of 26 patients modified their family planning because of the disease. Among the 80 students and teachers 45 were not aware of "Narcolepsy" and 53 were not aware of "cataplexy". The delay between the initial symptoms of the disease and the correct diagnosis, decreased gradually during the past decades, but after 2000 still remained on average at 2.34 years (SD=1.6) compared to 8.5 +/- 9.5 before 2000.
Conclusions: Even though living conditions for narcoleptic people in Switzerland have continuously improved, awareness among the public and in the medical community is inadequate, resulting in delayed diagnosis, and unnecessary burden of disease.

## K21 Dynamic effective connectivity of epileptic networks of Left versus Right Temporal lobe epilepsy using scalp EEG

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Objective: We aimed to analyze the dynamic behavior of epileptic networks through the study of effective connectivity using scalp EEG signals, in order to improve the understanding of pathologic neural activity in particular spikes, seizures, and their electro-clinical and cognitive manifestations.
Methods: In 16 patients, 8 with right temporal lobe epilepsy (RTLE) and 8 with left temporal lobe epilepsy (LTLE), we assessed the connectivity of large-scale cortical networks during interictal spikes and baseline periods (no pathological activity) at high temporal resolution, using high density (96-256 channels) EEG recordings. The cortical electric source activity was obtained for 82 cortical regions of interest (ROI) using an individual head model and a distributed linear inverse solution. A multivariate, time-varying (millisecond resolution), and frequency-resolved (1-100Hz) Granger causality analysis (Partial Directed Coherence) was applied to the source signal of all ROIs. In all patients, the results were validated by subsequent intracranial recordings or post-surgical outcome. A non-parametric statistical test was carried out to assess the difference in outflow in each ROI between both groups.
Results: The key driving structures were located in the medial temporal regions for both groups. Either in individual cases or group analyses, we observed an increase in information outflow from the key driver around the spike. A different driving pattern between LTLE and RTLE was also found. In LTLE the keys drivers were only on the ipsilateral side while in RTLE the key drivers were in both ipsilateral and

contralateral areas. The results were concordant with the post-operative MRI – the main driver overlapped with the removed region. Conclusion: EEG-based time-varying effective connectivity of epileptic spikes was able to identify the major contributors to interictal epileptic activity in both RTLE and LTLE, which was concordant with invasive electro-clinical findings. Furthermore, a different pattern of connectivity in LTLE and RTLE was observed. This enhanced characterization of the epileptic networks could have major clinical implications for tailoring resective, disconnective and functional surgery.

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## K22 Reducing the error: Regional effects of HRF basis functions on EEG-microstate informed fMRI

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Introduction: It is unclear to whether the classical canonical HRF is the best approach to study the association between microstates and hemodynamic response. In the present work, we aimed to compare two sets of HRFs for microstate-informed resting-state fMRI analysis: the standard canonical HRF (CA), and the HRFs extended by the two derivatives (CA+). We tested the hypothesis that the extended model CA+ including the temporal and dispersion derivatives that account for inter-subject and regional variability (±1 second) in the BOLD signal may have a positive effect on residual reduction in microstate-informed fMRI analysis on distinct brain regions.

Methods/Results: Fourteen healthy subjects (6f/8m, mean age 26±2.7 years) underwent simultaneous EEG/fMRI in a no-task condition. We have found that the model CA+ shows significantly lower residuals in visual and right auditory areas across subjects. Global mean residual difference of the significant voxels of the visual and right auditory cortex across all subjects was 0.01 (SD=0.02), while mean local maxima in the selected areas across subjects were 0.13 (SD=0.12).

Discussion: Albeit the global mean residual difference along entire visual and right auditory areas and along subjects is very small, mean local maximum values show significant large differences in specific voxels, suggesting that residual reduction is more likely to be regionally observed at the subject level, and to a lesser degree as a group level effect. These findings provide further support that the canonical HRF may be insufficient to explain variation of BOLD responses across brain regions and subjects. However, further investigation is needed to reduce residuals by using more flexible HRF models.

Declaration: This abstract was also submitted to the ISMRM annual meeting 2014.

## K23 Tracking sentence comprehension processes in healthy controls and aphasic patients

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Background: Aphasia is a common syndrome after left-lateralized stroke and is characterized by partial or total loss of language functions. Language production as well as language comprehension can be affected. Problems in sentence comprehension are often observed even in mildly aphasic patients. These problems become most evident when non-standard sentence structures are used. In a language like German for example, syntactic rules allow a relatively free order of the sentence parts and a construction with the object coming before the subject (so called non-canonical order) is possible. It has been shown that aphasic patients perform around chance level for such

sentences in sentence-picture-matching tasks. Diverging theories regarding the cause of this sentence processing deficit have been advanced, among others the Trace Deletion Hypothesis and the Slowed Processing Account. In addition to offline behavioural measures, eye tracking also sheds light on the online processing and can thus be helpful in gaining more insights about sentence processing deficits in aphasic patients.

Method: A sentence-picture-matching task with concurrent eye tracking was performed. Subjects heard a sentence and saw four different versions of a picture, one of them correctly depicting the sentence's content. The task was to indicate the correct picture by mouse click. The sentences differed with respect to their syntactic complexity. 50 healthy controls and 12 aphasic patients were tested.

Results: Healthy subjects showed an overall high performance, although they committed surprisingly many errors in the non-canonical sentences. As expected, aphasic patients performed worse overall, were slower and had pronounced difficulties in processing non-canonical and passive sentences. In correctly solved trials, healthy controls showed an increasing fixation preference for the target picture over time. Patients showed a similar pattern, but settled for the correct picture later. Furthermore, qualitatively different fixation patterns were found for the non- canonical sentences.

Conclusion: Sentence complexity affected the performance in both groups. Eye tracking data showed an overall slowed processing in aphasic patients as well as qualitative differences. These findings broaden our understanding of deficits in syntax processing.

## K24 Changes in cerebral blood flow following combined psychotherapy and cortisol treatment for spider phobia: a marker for treatment outcome?

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Neuroimaging techniques are increasingly applied to psychotherapy research, e.g. to identify changes in brain functions associated with emotion regulation after cognitive-behavioral therapy (CBT) of anxiety and specific phobias. In patients with spider phobia, feelings of fear at the exposure to spiders could be acutely reduced by previous pharmacological elevation of cortisol levels. Cortisol is normally released from the adrenal cortex under stress and modulates numerous cognitive and emotional processes, and diminished fear symptoms. In response to a phobic stimulus, the endogenous elevation of the cortisol level may represent an adaptive response. However, this mechanism is inhibited in spider phobia. Stress-induced increase of cortisol has been shown to be associated with changes in regional cerebral blood flow (rCBF) as measured by arterial spin- labeling (ASL), which is a quantitative and noninvasive neuroimaging technique. In this study we investigated if the therapeutic efficacy of exposure-based CBT is potentiated by the administration of cortisol and if these effects are correlated to changes in rCBF. ASL was measured in 15 patients with spider phobia before and 4 weeks after cessation of CBT. In a double-blind study design the patients were assigned to receive cortisol or placebo treatment. We could show that successful CBT - all patients showed significant reduction of fear symptoms at the follow-up ASL measurement - is associated with a significant decrease in rCBF in the prefrontal cortex. This effect is potentiated in patients treated with cortisol. Thus, cortisol treatment might facilitate the effects of CBT integrating exposure therapy by reducing fear symptoms at confrontation with the phobic stimulus. Insights into the neuronal mechanisms underlying effective treatment of spider phobia may provide important information for specified treatment of specific phobias and anxiety disorders.

## K25 Characterizing cognitive and functional outcome after cardiac arrest

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Introduction

The vast majority of studies assessing outcome after cardiac arrest (CA) use survival rate, with good outcome for survivors versus poor outcome for patients who die or remain with severe consciousness impairment. The aim of the present work is to prospectively specify cognitive and functional outcome of CA survivors - considered as good outcome - using a comprehensive neuropsychological assessment and quality of life evaluation.

Methods

Consecutive survivors after CA treated with therapeutic hypothermia between September 2012 and May 2013 were evaluated at 6 months follow-up. Patients participated to an exhaustive neuropsychological assessment using standardized tests representing 10 cognitive domains. Each domain was evaluated as “preserved” if less than 33% of tests were below 1.65 standard deviation from the mean of the reference population (z-score), vs. “impaired” if more than 33% of tests were below 1.65 standard deviation. Quality of life assessed subjectively on 6 dimensions (QOLIBRI) was described as “good” if less than 2 dimensions showed an unsatisfying score above 33% and “poor” if more than 2 dimensions showed an unsatisfying score above 33%.

Results

20/33 patients (61%) survived CA, and 15 (75% of survivors; 11 men; age 55.3 ± 14.2 years) were included. At 6 months, all patients lived independently at home; out of these 15 patients, 5 (33%) showed impairment in more than 2 cognitive domains (mainly reduced processing speed and attention deficits), and 4 of them had serious cognitive complaints; quality of life was evaluated as “poor” for 2 patients (13%).

Conclusion

While all patients were considered having good outcome and were independent for daily activities, neuropsychological and quality of life assessment was able to identify more subtle difficulties for a substantial number of patients. This refined evaluation will help characterizing cognitive profile and specific needs of cardiac arrest survivors.

## K26 Discovering resting EEG microstate abnormality in semantic dementia

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Semantic dementia, a variant of the frontotemporal lobar degeneration is characterized by a loss of word meaning, manifested by progressive language disorder such as impaired naming or empty spontaneous, but fluent speech. Diagnosis of semantic dementia relies still on costly MRI or PET neuroimaging methods, although resting EEG markers of for instance Schizophrenia, frontotemporal dementia and Alzheimer’s disease have been reported. In order to close this gap, the current study analyzed the common four resting EEG microstate classes (A, B, C, and D) of patients with semantic dementia in comparison with healthy controls and patients with Alzheimer’s disease. A topographical analysis revealed that both dementia group lacked of the specific microstate class C commonly found in healthy

adults. Instead, they had a different microstate that the healthy controls did not show. While microstate classes A and D were comparable between all groups, microstate class B differed between patients and controls, although the pattern appeared similar. Furthermore, the ratio of how often the microstate classes occurred across groups was tested. The statistics revealed that class B occurred significantly more often in semantic dementia than in the healthy and Alzheimer groups. Taken together, this is the first study that discovered resting state EEG abnormality in semantic dementia. However, topographic comparison of microstate classes alone is not able to distinguish between semantic dementia and Alzheimer's disease. Nevertheless, combining the topographic analysis with the comparison of the ratio of the classes might prove to be an apt and economic approach to refine the differential diagnosis of dementia.

## K27 Effect of carotid stenosis treatment on cognitive functions

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Aim: To evaluate cognitive changes in patients with carotid artery stenosis according to the treatment type (endarterectomy, stenting, best medical treatment). Current literature yields divergent results regarding the effects of different carotid stenosis treatment types on cognitive functions. We hypothesized that treatment of the carotid artery leads to an improvement of cognitive performance and analyzed the therapy effects based on the type of treatment.

Methods: Sixty patients (mean 69.5 years) with asymptomatic or mildly symptomatic extracranial carotid artery stenosis >70% were included. Patients performed neuropsychological assessments before treatment (TP1) with carotid endarterectomy (n=20), stenting (n=10) or best medical treatment (n=30), and one year later (TP2). Executive functions, language skills (verbal fluency, word production), visual and verbal memory, and the emotional state were assessed. Changes in cognitive performance between TP1 and TP2 were analyzed building a relative gain score (performance at TP2 – performance at TP1 / performance at TP1).

Results: There were no significant differences between the three treatment groups regarding age, gender, education, stenosis side, risk factors and performance at TP1. Irrespective of the treatment modality patients showed significantly better relative gain score in executive function (Inhibition: $p=.011$), verbal fluency ($p=.010$), verbal short term memory ($p<.001$) and visual memory ($p=.003$). There were no significant changes in word production and emotional state after one year. Changes in cognitive performance did not differ between the three treatment groups in any of the applied cognitive tests.

Conclusions: These preliminary results highlight the potential positive effect of active treatment of carotid stenosis on cognitive performance irrespective of the choice of treatment whether best medical treatment, endarterectomy or stenting.

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