19th Annual Meeting
of the
Swiss Society for Neuroscience
together with the
Neuroscience Network Basel

Friday January 27th 2017
Zentrum für Lehre und Forschung,
University Basel
Hebelstrasse 20, 4031 Basel

Registration, abstract submission and further information:
www.swissneuroscience.ch/ssn-activities/annual-meeting
Abstract submission deadline 16.01.2017
## Program

09:00 - 09:45  Registration and Poster setup
09:45  Welcome and Opening remarks: SSN President and Vice Rector Uni Basel  (grosster Hörsaal)

### PLENARY LECTURE 1 supported by the Synapsis Foundation, chair: Verdon Taylor

10:00 -10:45  Hongjun Song  (John Hopkins, USA)  *Single-cell analysis of mammalian neural stem cells and neurogenesis*

10:45 -11:10 Coffee Break

In parallel 11:10 – 12:30:  Symposium 1 grosster Hörsaal; Symposium 2 kleiner Hörsaal

### SYMPOSIUM 1: DEVELOPMENT AND MATURATION OF NEURONAL CIRCUITS

*Chaired by:* Tania Rinaldi Barkat (DBM, Basel)

11:15 -11:40  Oscar Marin  (KCL, London)  *Molecular regulation of cortical interneuron diversity and plasticity*
11:40 -12:05  Denis Jabaudon  (Uni Geneva)  *Becoming a new neuron in the cerebral cortex*
12:05 -12:30  Sonia Garel  (ENS, Paris)  *Microglia and prenatal inflammation in the development of cortical inhibitory circuits*

### SYMPOSIUM 2: CORTICAL PROCESSING IN RODENTS, MONKEYS AND HUMANS

*Chaired by:* Georg Keller (FMI, Basel)

11:15 -11:40  Jakob Heinzle  (ETH, Zuerich)  *What can fMRI tell us about cortical processing?*
11:40 -12:05  Adam Kampff  (SWC, London)  *Cortex + CMOS: Distributed, whole-brain, single-unit electrical recordings*
12:05 -12:30  Valerio Mante  (INI, Zuerich)  *Prefrontal population dynamics underlying deliberation, decisions, and actions*

12:30 -14:45 Poster Session & Lunch
13:30 -14:30  SSN Business Meeting: financial report and election of new council members  (grosster Hörsaal)

### PLENARY LECTURE 2  chair: Sonja Hofer  (grosster Hörsaal)

14:45 -15:30  Rodrigo Quian Quiroga  (Leicester, UK)  *Concept cells and their role in memory*

15:30 -15:45 Coffee Break

In parallel 15:45 – 17:05:  Symposium 3 grosster Hörsaal; Symposium 4 kleiner Hörsaal

### ySSN SYMPOSIUM 3: NEURONAL REGENERATION AND REPAIR

*Chaired by:* youngSSN

15:50 -16:15  Fiona Doetsch  (Biozentrum, Basel)  *Local and long-range niche regulation of adult neural stem cells*
16:15 -16:40  Martin Schwab  (Uni Zuerich)  *Traumatic CNS injuries: How to bring back function*
16:40 -17:05  Anne Rosser  (Cardiff University)  *Cell replacement for Huntington’s disease: progress and challenges*

### SYMPOSIUM 4: NEURONAL CIRCUIT MECHANISMS FOR BEHAVIOR AND LEARNING

*Chaired by:* Andreas Luethi (FMI, Basel)

15:50 -16:15  Daniel Huber  (Uni Geneva)  *Probing cortical function with neuroprosthetic learning*
16:15 -16:40  Cyril Herry  (INSERM, Bordeaux)  *Prefrontal circuits encoding context fear discrimination*
16:40 -17:05  Benjamin Grewe  (INI, Zuerich)  *The ups and downs of hebbian plasticity in associative learning*

17:10 –17:30  SSN Poster and Publication Awards and closing remarks of new SSN President  (grosster Hörsaal)
Directions to ZLF
(Zentrum für Lehre und Forschung),
University Hospital Basel

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

By car:
Highway Basel City, then follow direction University Hospital (Universitätsspital). Parking possible in Parking City.
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Wyss Center for Bio and Neuroengineering
A1 The pharmacological blockade of the Na+/Ca2+ exchanger modulates the growth and development of the Purkinje cell dendritic arbor in mouse cerebellar slice cultures

Authors
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The Na+/Ca2+ exchanger (NCX) is a bi-directional plasma membrane antiporter involved in Ca2+ homeostasis in eukaryotes. NCX has three isoforms, NCX1–3, and all of them were expressed in Purkinje cells, with NCX1 being the most abundant. The pharmacological blockade of the forward mode of NCX (Ca2+ efflux mode) by Bepridil moderately inhibited growth and development of the Purkinje cell dendritic arbor in cerebellar slice cultures. However, the blockade of the reverse mode (Ca2+ influx mode) by KB-R7943 severely reduced the dendritic arbor and induced a morphological change with thickened distal dendrites. The effect of KB-R7943 on dendritic growth was unrelated to the activity of voltage-gated calcium channels and was also apparent in the absence of bioelectrical activity indicating that it was mediated by NCX expressed in Purkinje cells. We have also used additional NCX inhibitors like CB-DMB, ORM-10103, SEA0400, YM-244769 and SN-6 which have higher specificity for NCX isoforms and target either the forward, reverse or both modes. These inhibitors caused a strong dendritic reduction similar to that seen with KB-R7943 except for thickened distal dendrites.

Our findings indicate that the disturbance of the NCX-dependent calcium transport in Purkinje cells induces a reduction of dendritic development which is most likely caused by changes in the calcium handling of Purkinje cells. They underline the importance of the calcium equilibrium for the control of dendritic development in cerebellar Purkinje cells.

A2 Neurogenic Stem Cells in a Dormant Niche are Activated by Antidepressant Fluoxetine and Suppressed by Notch2 Signaling

Authors
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Age-associated declines in tissue homeostasis and regeneration correlate with reduced stem cell activity. In most regions of the mammalian brain, neuron production stops soon after birth.

Notch signaling is known to be essential in adult neural stem cell (NSC) maintenance. It previously was shown that loss of Rbpj, the downstream mediator of Notch signaling, results in a loss of all NSCs, whereas the loss of Notch1 only resulted in the loss of active NSCs. In a comparative in vivo study we analysed the distinct effects of deletion of Notch1, Notch2, Rbpj and a compound deletion of Notch1 and Notch2 on murine adult NSCs.
We hereby identified bona fide neural stem cells (NSCs) outside the classical neurogenic zones and identify a novel population of NSCs in their niche, the dorsal septum. Resident septal NSCs are held in a dormant state but retain neurogenic potential, responding to antidepressants to generate new neurons in vivo. Notch2 but not Notch1 signaling conveys quiescence to these stem cells and their subventricular zone counterparts, repressing cell cycle-related genes and neurogenesis. Loss of Notch2 activates quiescent NSCs to proliferate and generate new neurons. Thus, NSCs in- and outside the classic germinatal zones of the brain are held in a reversible, inactive state by Notch2 signals.

A3 The role of canonical Wnt signalling in dendritogenesis of retrosplenic cortex neurons

Authors
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Dendritogenesis and synaptogenesis are key events of neuronal circuit formation that are finely regulated in time by a multitude of signalling pathways. Several neurodevelopmental disorders arise from an imbalanced neuronal network, which can be consequence of deregulated dendritic and synaptic formation. In particular, retrosplenic cortex (RSC) dysfunction has been linked to bipolar disorder, schizophrenia and autism. Here, using a combination of in utero electroporation and iontophoretic injection, we investigated the role of canonical Wnt signalling in dendritic development and spine formation of layer II cortical pyramidal neurons in the rat RSC. We found that canonical Wnt signalling level increases at the beginning of dendritogenesis and is required for the development of proper dendritic arborization. Disruption of the signalling pathway during a specific, early postnatal time window results in defective dendritic formation that is irreversible and persists until adulthood. At later time points, Wnt signalling is not necessary for maintaining a correct dendritic arborization, however Wnt LOF results in decreased spine and synapse densities. We identified neurotrophin-3 (NT3) as a new downstream target of canonical Wnt pathway, the overexpression of which rescues both dendritic arbor defect as well as spine density. Together, these results reveal a role for canonical Wnt signalling in dendritic arborization of layer II neurons in vivo and suggest a function in RSC circuit formation.

A4 Delayed neuronal migration alters interhemispheric connections causing autism-like behavior

Authors
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Perturbed neuronal migration has been implicated in the pathogenesis of human neurodevelopmental diseases such as autism spectrum disorder; however, the developmental steps leading to behavior alterations remain unknown. Here we demonstrate that Wnt/C-Kit signaling is a key regulator of glia-guided radial migration in rat somatosensory cortex. A transient down-regulation of this signaling in migrating, callosal projection neurons results in delayed positioning in layer II/III. Delayed neurons display reduced afferent connectivity and lower neuronal activity causing permanent deficit in callosal projections. Animals with these defects not only exhibit altered somatosensory function but also reduced social interactions and repetitive movements. Restoring normal migration by over-expressing the Wnt-downstream effector C-Kit prevents abnormal interhemispheric
connections as well as behavioral alterations. Moreover, reduced callosal connectivity can be rescued by exclusive chemogenetic activation of callosal projection neurons during a critical postnatal period. Our findings identify a mechanistic link between the transient delay of neuronal migration, deficient interhemispheric connectivity and abnormal social behavior that may be analogous to autistic characteristics in humans.

**A5 Neonatal hypoxia-ischemia in rat disrupts the developmental time course of doublecortin release in the cerebrospinal fluid**

**Authors**
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Introduction: Doublecortin (DCX) is commonly used as a marker of neurogenesis in immunohistochemical (IHC) stainings of adult rodent brains. Using a recently developed immunoassay that enables objective quantification of DCX in tissues and body fluids, we examined whether DCX in the cerebrospinal fluid (CSF) may be a valid indicator of endogenous neurogenesis. This question was addressed in the rat model of neonatal hypoxia-ischemia (HI), a brain injury documented to stimulate neurogenesis. Methods: HI was elicited at postnatal day (P) 7 in Sprague-Dawley rats via ligation of the right common carotid artery and 40 minutes exposure to 8% O2. Control animals received a sham surgery without HI. CSF was collected serially from the cisterna magna at P5 and P10, or at P10 and P15. Bromodeoxyuridine (BrdU) was administered intraperitoneally from P7 to P9 to label dividing cells, and P10 brains were processed for IHC analyses. Results: In sham-exposed neonates, a sharp, significant drop in the mean concentration of DCX in the CSF (CSF-DCX) occurred between P5 and P15. In HI-exposed neonates, CSF-DCX increased significantly between P5-P10, but declined between P10-P15; yet, at P15, CSF-DCX remained significantly higher in HI than in control neonates. In the P10 HI group, CSF-DCX correlated positively with stroke severity. DCX immunointensity and the number of BrdU-positive cells were significantly increased in the ipsilateral neurogenic niches from P10 HI neonates in comparison to that from age-matched sham neonates. DCX expressing cells were negative for cleaved caspase-3, a cellular death marker, in both groups. Conclusions: Neonatal HI brain injury remarkably disrupts the developmental time course of DCX release in the CSF. The data indicate that the increase in CSF-DCX after neonatal HI reflects both injury-associated cell death and injury-associated neurogenic response.

**A6 Erythropoietin accelerates postnatal maturation of GABAergic neurons**

**Authors**
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Erythropoietin (Epo) is a hypoxia inducible hormone, highly expressed in the neural tube during embryonic and fetal development, abruptly reducing its expression postnatally. Epo is mainly known for its systemic role in red blood cell formation and its central neuroprotective anti-apoptotic and anti-inflammatory effects. However, its function in the developing central nervous system remains elusive. Our previous work has demonstrated that constitutive cerebral overexpression of Epo (Tg21 mice) can accelerate postnatal brain maturation.
Here, we first elucidated the effect of Epo on proliferation and neuronal differentiation in rat neuronal hippocampal cultures across 3 to 18 days in vitro (3-18 DIV) using markers of neuronal proliferation (Ki67) and neuronal differentiation stages: Neural Stem Cells (NSC, nestin); migratory immature neurons (Doublecortin X, DCX) and mature neurons (Microtubule Associated Protein 2, MAP2).

The role of Epo in postnatal maturation of the GABAergic neurons was morphologically evaluated in the hippocampus of the Tg21 and WT mice. We analyzed the time window of expression of Parvalbumin (PV), Somatostatin (SOM), Neuropeptide Y (NPY) and Calbindin (CB) from P3 to adulthood (P60). Expression of PV, SOM and NPY appeared earlier in the Tg21, unlike CB.

Our in vitro results show that addition of Epo to the media mainly allows the maintenance of a proliferating pool of immature neurons (Ki67+/Nestin+). Moreover, the Tg21 mice exhibit a faster rate of maturation in specific GABAergic neurons.

A fatty acid oxidation-dependent metabolic shift regulates adult neural stem cell quiescence

Authors
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Neural stem/progenitor cells (NSPCs) generate new neurons throughout life in distinct regions of the mammalian brain. Adult neurogenesis is important for tissue homeostasis and physiological brain function, and disturbed neurogenesis has been associated with diseases such as major depression and epilepsy. A tight regulation of NSPC quiescence and proliferation is crucial to ensure life-long neurogenesis and prevent exhaustion or uncontrolled growth of the stem cell pool. What regulates this delicate balance is not fully understood. Here we show that the rate of lipid breakdown via fatty acid oxidation (FAO) defines quiescence vs. proliferation in NSPCs. Quiescent NSPCs show high expression of the key enzymes regulating FAO, such as for instance carnitine palmitoyltransferase 1a (Cpt1a). Pharmacological inhibition and conditional deletion of Cpt1a in vitro and in vivo leads to altered NSPC behavior, reducing stem cell maintenance and proper neurogenesis. Strikingly, experimental manipulation of a single metabolite that regulates levels of FAO, is sufficient to induce exit from quiescence and to enhance NSPC proliferation. Thus, the data presented here define a metabolically controlled mechanism of quiescence behavior and reveal an instructive role for fatty acid metabolism in regulating NSPC activity.
Impact of Fibrin Matrix on Directing Neural Stem Cell Fate

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Background: Neural stem cell transplantation represents a promising therapy after stroke. But since transplantation of cells into a lesion cavity of the central nervous system (CNS) is associated with huge initial cell death, tissue engineered scaffolds are supposed to provide a supportive environment for the transplanted cells. In this context, fibrin is a promising scaffold to treat CNS injuries due to its biocompatible and biodegradable properties.

Methods: Human neural stem cells (huNSCs), derived from human embryonic stem cells, were seeded on fibrin matrices and cultured in vitro. As a control, huNSCs were cultured on a 2D substrate without fibrin. The cell viability and proliferation was then measured repeatedly for 61 days. At the same time points, the culture medium was collected and frozen. Additionally, cells were fixed and stained after being cultured in fibrin between 15 and 53 days. Images were acquired with a confocal microscope.

Results: Although the controls had higher viability and proliferation values at any time point, our results show that the huNSCs stayed viable for up to 61 days. An increase in proliferation can be observed in the fibrin condition after 31 days, having steadily high viability values afterwards until day 61.

The microscopic images indicate that the neural stem cells are spread throughout the matrix.

Conclusion: The fact that the cells stay viable for many days in the fibrin scaffold, supports the hypothesis that fibrin represents a promising scaffold for transplantation of neural stem cells. Other experiments are under progress to further investigate cell survival.

Effects of Single or Repeated Intranasal Administration of Umbilical Cord Stem Cells in Neonatal Rats with Hypoxic-Ischemic Brain Lesions

**Authors**
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Lately, there has been a significant increase in preterm-specific brain injuries that still remain an unresolved clinical issue. The majority of the infants born preterm with brain injuries develop non-cystic, diffuse white matter injury (WMI), characterized by an overall hypomyelination of the brain. Preterm brain injury is an important cause of long-term disability. To date, no cure has been found to treat such lesions. Intranasal delivery of Wharton’s jelly mesenchymal stem cells (WJ-MSC) might be the ideal, non-invasive therapeutic approach to restoring the damaged brain. Therefore, our goal is to find an optimal treatment regimen of intranasally delivered WJ-MSC to achieve a maximum recovery after brain injury.

WJ-MSC (84’000 cells/l) were delivered intranasally to Wistar rat pups that were previously brain-damaged (total 1*106 cells). Rat pups received either one, two or three treatments, at two days intervals. Animals were
sacrificed 7 days after the first application of the cells. Fixed brains were analyzed by immunohistochemistry, real-time PCR, and electron microscopy. Proteins from fresh frozen tissue were used for western blotting.

Intranasal delivery of WJ-MSC increased myelination and decreased astro- and microgliosis. Repeated intranasal delivery was not more effective than single treatment, as assessed by immunohistochemistry. Nonetheless, multiple administrations increased significantly the expression of important neurotrophic factors like brain-derived neurotrophic factor or vascular endothelial growth factor.

In conclusion, intranasal delivery of WJ-MSC to the newborn after preterm brain damage has a neuroregenerative potential, which is probably mediated by a decreased astro- and microgliosis and an increased expression of important neurotrophic factors like Bdnf. Intranasal delivery of stem cells to the brain is an efficient and non-invasive method for stem cell treatment of perinatal brain damage.

Financial support by Cryosave Switzerland, Mobiliar Jubiläumsstiftung, Switzerland and The Eagle Foundation, Switzerland.

A10 Quantitative analysis of the structural development of the monkey entorhinal cortex.

Authors
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Recent studies have shown that different hippocampal circuits exhibit distinct developmental profiles, which may subserve the emergence of specific “hippocampus-dependent” memory processes. Since the entorhinal cortex is the main interface between the neocortex and the hippocampus, we aimed to characterize its postnatal development in monkeys. Its superficial layers II and III send feedforward projections to the dentate gyrus and the hippocampus, while its deep layers V and VI receive feedback projections from CA1 and the subiculum. Additionally, layer III receives projections from the presubiculum. The entorhinal cortex comprises seven subdivisions characterized by different interconnections with other brain regions, including the hippocampus. We found no differences in neuron number in any subdivisions of the entorhinal cortex between newborn and adult monkeys. However, we found differences in neuronal volumes, which were specific to certain layers and subdivisions. In rostral areas (Eo, Er and Ei), we found no age differences in volume of layer III neurons, but an increase in volume of layer V neurons between birth and adulthood. In caudal areas (Ec and Ecl), we found that the volume of layer III neurons decreased from birth to adulthood, while the volume of layer V neurons increased from birth to adulthood. Our findings suggest: (1) an early maturation of the superficial layers of the entorhinal cortex, the main input pathways to the hippocampus; (2) an early maturation of the projections from the presubiculum to the caudal entorhinal cortex; and (3) a late maturation of the projections originating in CA1 and the subiculum.
Maternal overnutrition alters the development of the mesolimbic reward system and hedonic behaviors in the offspring across generations

Authors
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Introduction
Maternal overnutrition during critical periods of development was shown to be a risk factor for the development of obesity and neuropsychiatric disorders in the progeny. Studies in animal models suggest that maternal overnutrition alters the central reward system in such a way that it affects offspring’s hedonic behaviors by increasing their preference for palatable food as well as to drugs of abuse. However, it remains unknown, whether these alterations in brain and behavior following maternal overnutrition can be transmitted to subsequent generations. To this end, we were interested in studying the long-term effects of maternal overnutrition (high fat diet, HFD, exposure) in mice on the mesolimbic brain reward system, in particular the dopaminergic circuitry, and the sensitivity to drugs of abuse across multiple generations.

Materials and methods
Female dams were exposed to either HFD or laboratory chow 3 weeks prior to mating, 3 weeks during gestation and 3 weeks during lactation. Offspring (first generation, F1) born to either HFD or chow food exposed dams were on chow diet after weaning. F1 male offspring from both HFD and chow food exposed dams were mated with naive female to generate second generation F2 offspring. Both F1 and F2 offspring were evaluated in behavioral, neuroanatomical and neurochemical tests.

Results
To evaluate the sensitivity to drugs of abuse, we tested the offsprings’ response to a low dose of amphetamine. Both F1 and F2 offspring of HFD exposed dams displayed enhanced locomotor response to the drug as compared to offspring born to chow fed dams. Our results show that in a naive cohort of animals, both F1 and F2 offspring of HFD exposed ancestors display (1) lower tyrosine hydroxylase (TH) expression in the ventral tegmental area (VTA) and (2) higher dopamine 2 receptor (D2R) levels in the nucleus accumbens (NAC) and the dorsal striatum (DSTR) (determined by immunostaining). Further, post-mortem neurochemical analysis reveal that maternal HFD leads to significantly reduced levels of dopamine in the NAC and the DSTR in F1 and F2 offspring suggesting lower dopamine tone in the striatal regions.

Conclusion
Together, our results for the first time report that perinatal maternal high fat diet exposure causes permanent alterations of the function of the mesolimbic dopaminergic system which is persistent in the progeny up to second the generation suggestive of a predisposition to develop addictive-like behaviors across generations.

Calyntenin1-mediated vesicular trafficking of guidance receptors at choice points is required for a proper axon guidance

Authors
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In neural circuit formation, neurons send out axons through a constantly changing environment to reach the
proper targets. The contact between the growth cone and intermediate targets is required to direct axons toward their final target. At these choice points, a precise regulation of guidance receptors is needed to change their responsiveness from attraction to repulsion and, thus, for the continuation of their migration. To study the underlying mechanisms of this switch in behavior, the dI1 (dorsal interneuron1) subpopulation of commissural neurons in the spinal cord have been used as a model. The dI1 axons project ventrally towards the floor plate, a well-known intermediate target. After crossing the midline and crossing the floor plate, axons turn rostrally along the longitudinal axis of the spinal cord.

A precise temporal control of growth cone receptor expression is crucial during axon guidance. Thus, we study the role of vesicular trafficking of key receptors during axon guidance. Calsyntenins are a family of three proteins able to bind to Kinesin motors and act as cargo-docking proteins in vesicular transport along axons. Their dynamic expression during neural circuit development is compatible with a role in axon guidance. Indeed, our results show that Calsyntenin1 is required for the transport of Robo1-containing vesicles to the growth cone surface in a precisely regulated manner. The presence of Robo1 on the growth cone triggers sensitivity to the midline-associated repellent Slit1 during midline crossing. Consequently, axons can exit from the floor plate and continue with their journey. In addition, Calsyntenin1-mediated trafficking of Frizzled3, a key receptor in the Wnt pathway, controls rostral navigation of post- but not pre-crossing axons. Our results suggest that a tightly regulated insertion of guidance receptors is required for proper axon guidance, and that this is achieved by specific Calsyntenin1-mediated vesicular trafficking.

B. Synaptic Plasticity, Neurons and Glia

B1 GABAergic synapse plasticity affects hippocampal dependent memory formation

Authors
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Inhibitory neurotransmission mediated by gamma amino butyric acid (GABA) neurotransmitter is key to balance excitatory transmission and synchronize neuronal circuits. It allows the generation of oscillatory activities and the emergence of cell assemblies that underlie cognitive processes such as learning and memory. GABAergic synapses are plastic and undergo activity-dependent changes in efficiency and structure. Structural plasticity of excitatory synapses is critical for learning and memory formation but the role of structural remodeling of GABAergic synapses in mnemonic processes is still largely unknown. Gephyrin, the main scaffolding protein at GABAergic synapses, orchestrates molecular interactions required for proper synaptic function and plasticity. Recent studies have shown that learning related neuronal activity triggers N-Methyl-D-Aspartate (NMDA) receptor activation and Ca2+/calmodulin-dependent protein kinase II (CaMKII) phosphorylation of Gephyrin that ultimately induces structural remodeling of GABAergic synapses (Flores et al., 2014). In the present work we manipulate CaMKII-dependent phosphorylation of Gephyrin to assess its role in GABAergic synapse functional and structural plasticity and the impact on hippocampal-dependent memories.

B2 Aberrant behavior and synaptic pathology in the Sapap3-/- mouse model of obsessive-compulsive disorder

Authors
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Affiliations
Obsessive-compulsive disorder (OCD) often resist conventional treatment such as selective serotonin uptake inhibitors. The identification of the underlying circuit-pathology may reveal novel targets for mechanism-based OCD treatment strategies. Here we assessed behavioral phenotypes of the Sapap3-/- mouse model for OCD, and characterized the excitatory synapses of projections from the orbitofrontal cortex (OFC) to dorsal striatum. In an operant lever-press task with sucrose as reward, WT mice exhibited goal-directed behavior whereas the Sapap3-/- mice showed habitual actions after a two-week training period. Over-grooming and significantly decreased locomotor activity was also evident in Sapap3-/- mice. On the cellular level, we found decreased synaptic strength for the input from the OFC to D2-MSNs in the dorsal striatum, quantified by a decreased AMPA/NMDA ratio in Sapap3-/- mice compared to WT. In future experiments, we will assess if depotentiated OFC input underlies OCD-like behavior in the Sapap3-KO mice, using optogenetic reversal of plasticity.

B3 Resolving accumbal projections to lateral hypothalamus

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Nucleus accumbens (NAc) inhibits several downstream targets, including the ventral pallidum, lateral hypothalamus (LH) and ventral midbrain. Our previous work has shown that NAc medium-sized spiny neurons projecting to LH predominantly express the dopamine D1 receptor (D1-MSNs) and inhibit LH GABA neurons to control food consumption. Here, using neural tracing and in vitro electrophysiology in transgenic mouse lines that permit identification and activity control of specific cell types, we further dissect the connectivity and synaptic plasticity of this pathway. First, we find that the few D2R-MSNs innervating LH have cell bodies located in the most posterior aspect of NAc and target the anterior aspects of LH. Second, in addition to LH GABA neurons, D1R-MSNs are found to monosynaptically inhibit LH glutamate neurons and LH neurons projecting to the lateral habenula, but rarely LH orexin neurons. Finally, in contrast to NAc projections to the pallidum and midbrain, inhibitory synapses between D1R-MSNs and LH fail to undergo high frequency stimulation induced long-term potentiation (HFS-LTP). Taken together, our data challenge the traditional view of direct and indirect pathways as applied to ventral striatal circuitry and suggest distinct properties of NAc to LH inhibitory synapses that may hold relevance in the control of motivated and emotional behavior.

B4 Synaptic plasticity underlying compulsive reinforcement

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Addiction is defined by the perseverance of drug consumption despite harmful consequences. This is seen as a compulsive behaviour to obtain reinforcement and can be observed in rodents using a reward/punishment evaluation task. In this study, we use optogenetic self-stimulation of Ventral Tegmental Area dopamine neurons to reinforce behaviour. In addition, anatomical tracing methods, slice electrophysiology and behavior allow characterization of neuronal circuit alterations associated with the development of compulsive reinforcement. Akin to drug-addiction, we found that only a subset of mice develops compulsivity for optogenetic self-stimulation of the VTA. In compulsive animals, a number of neuronal adaptations were observed. Specifically,
pyramidal neurons of the Orbitofrontal Cortex (OFC) were more excitable because of alteration of the excitation/inhibition ratio. Chemogenetic inhibition of the Submedius Thalamic Nucleus or the Basolateral Amygdala, two structures sending dense projection to the OFC, alter the expression of compulsivity via changed in neuronal excitability. Downstream from the OFC, synaptic strength to the dorsal striatum again correlates with the degree of compulsivity. We believe that characterization of synaptic adaptations underlying the expression of a compulsive behaviour towards reinforcement represents a necessary step to understand individual vulnerability to addiction.

B5 Coupling of the glutamate-glutamine cycle rate with both glial and neuronal oxidative metabolism in the visual cortex of the Tupaia belangeri

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Cerebral function relies on cooperative interaction between neuronal and glial cells. While neuronal oxidative metabolism has been shown to be coupled to the glutamate-glutamine cycle that represents glutamatergic neurotransmission, it remains unclear whether similar coupling occurs for glial oxidative metabolism. We took advantage of the columnar characteristics of the Tupaia belangeri primary visual cortex (V1) to measure metabolic changes induced by continuous stimulation of V1 using 13C after anatomical MRI, each animal (n=5 in the stimulation and n=4 in the resting group) under light isoflurane anesthesia (0.5-0.7%) underwent the three MR modalities at 14.1 T, namely blood oxygenation level-dependent functional magnetic resonance imaging (BOLD fMRI), 1H and 13C MRS localized in V1, either at rest or during stimulation. The visual stimulation device was composed of 2 matrices of 64 light-emitting diodes each. The paradigm consisted of delivering lines in 4 orientations and 2 directions at 5 and 7 Hz randomly switched. Each pattern with spatial frequency 0.04-0.05 cycle/degree was presented for at least 5 s. The luminosity corresponded to 48±4 LUX at 1 cm distance from the eyes of the animal. Visual stimulation resulted in a relatively large activated area in V1 that allowed localized MRS. Cortical brain activity resulted in a decrease in both brain glucose concentration (-17%; -0.34 µmol/g; P<0.001) and phosphocreatine/creatine ratio (-9%; -0.07; P<0.05) after 15 minutes of stimulation. At the individual level, close relationships between the neurotransmission rate (VNT) and total cerebral metabolic rate of glucose oxidation (CMRglc(ox), R2=0.68, P=0.006), glial (VTCAg, R2=0.66, P=0.008) and neuronal (VTCAn, R2=0.40, P=0.066) oxidative metabolism was measured. At the group level, 20% increase in VNT (+0.038±0.042 µmol/g/min, P=0.077) resulted in a 24% (VTCAg=0.063±0.057 µmol/g/min; P=0.007) and 12% (VTCAn=0.061±0.032 µmol/g/min; P<0.001) increase in glial and neuronal TCA cycle activity, respectively, resulting in a net 14% increase in CMRglc(ox) (+0.058±0.032 µmol/g/min; P<0.001).

We conclude that cortical brain activity resulted in a significant increase in cerebral metabolic rate of glucose consumption, which was associated to an increase of similar amplitude of both glial and neuronal oxidative metabolism that scaled with the glutamate-glutamine cycle rate.
**B6** Imaging extracellular potassium dynamics in brain tissue using a potassium sensitive nanosensor

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Neuronal activity results in the release of K+ into the extracellular space (ECS), which alters the potassium equilibrium potential and modulates further activity. In order to analyze these potassium dynamics and their role in the brain we designed and characterized a fluorescent K+-sensitive nanosensor for the ECS based on dendrimer nanotechnology. The nanosensor was assessed by spectrofluorimetry, including for its spectral properties, its sensitivity, and its selectivity, demonstrating the nanosensor’s efficacy over the physiologically relevant ion concentration range. Spatial and temporal kinetics of the nanosensor responses were assessed using localized iontophoretic K+ application on a two-photon imaging system. We also demonstrate that the nanosensor is retained in the ECS of acute mouse brain slices for extended periods of time, and validate its sensitivity in brain tissue in response to elicited neuronal activity, correlating this to extracellular field potential.

**B7** Systematic investigation of the roles of proteins with calcium-binding domains in synaptic transmission and presynaptic calcium buffering

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Changes in intracellular concentration of free calcium are the most diverse way of regulating intra- and intercellular signaling. Calcium ions entering a nerve terminal upon AP-stimulation are rapidly bound by proteins with calcium-binding domains (CaBPs). Maladaptive calcium-homeostasis and several CaBPs have been linked to neurological disorders, making it important to understand how CaBPs regulate synaptic transmission. We used an electrophysiology-based RNAi screen at the Drosophila neuromuscular junction to unravel the roles of presynaptic CaBPs in neurotransmitter release. Specifically, we quantified synaptic transmission after presynaptic overexpression of RNAIs targeting 213 CaBP-genes, most of which encode EF-hand and/or C2-calcium-binding domain. This screen identified several candidate mutants with increased or decreased synaptic transmission without apparent changes in synapse morphology. We are in the process of analyzing candidates in terms of genetics, presynaptic calcium dynamics, synaptic physiology and morphology. This approach is expected to reveal new insights into the basic mechanisms of presynaptic calcium-signaling and its role in neural physiology and pathology.
Accumbal SHANK3 downregulation boosts D1-MSN pathway and generate social dysfunction

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Accordingly to the DSM-V, the two core symptoms of Autism Spectrum Disorders (ASDs) are social contact and communication deficits, as well as stereotyped and restricted behaviours. One of the main genetic causes of ASDs are mutations in the coding region of SHANK3, a post-synaptic protein linking ionotropic and metabotropic glutamate receptors. Studies on ASD patients showing reduced social reward-related activation of the Ventral Striatum and the enriched content of SHANK3 in the region, point to the Nucleus Accumbens (NAc) as an intriguing target for translational research. In order to establish a causal link between NAc excitatory transmission impairment and ASD-related symptoms, we postnatally downregulated SHANK3 in the NAc (NAc-SHANK3) and assessed its consequences on glutamatergic transmission in mice. By combining viral infections with transgenic lines, we found enhanced AMPA transmission and increased intrinsic excitability of D1R-expressing MSNs (D1-MSNs) at late adolescence and adulthood. Moreover, NAc-SHANK3 mice showed deficits in social interaction without changes in anxiety-like behaviour parameters. These results indicate that SHANK3 downregulation restricted to NAc boosts D1-MSN pathway and generate ASD-like behavioural symptoms.

The Ventral Posterolateral Nucleus: Physiological, Morphological, and Somatotopic Properties

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The ventral posterolateral (VPL) nucleus of the thalamus serves as a relay center for the somatosensory system, receiving various forms of tactile and proprioception information from the periphery. These sensory signals are known to be mapped onto the somatosensory cortical surface in a topographic point-for-point correspondence. The VPL, a subcortical input to the somatosensory cortex, has also been observed to exhibit a similar somatotopy, and thus, we hypothesized a corresponding distribution of the physiology, morphology, and connectivity of the neurons. Here, we systematically investigated the electrophysiological and morphological characteristics of the VPL in rats of age postnatal 14-18 days. We obtained whole cell multi-patch clamp recordings of VPL relay cells in acute slices and stained and morphologically reconstructed the neurons. We also observed short term plasticity responses of VPL relay cells in various locations with medial lemniscus electrical stimulation. The VPL relay cell data is being integrated into the in silico model of the rat somatosensory cortex (Markram et al. 2015) to reconstruct and simulate this thalamocortical pathway. We explored how the heterogeneity of functional and morphological properties of the VPL and their connectivity properties may impact sensory perception.
A neuron's response to presynaptic activity is shaped by the short-term plasticity (STP) at its afferent synapses. Therefore, the distribution of STP of the synapses that converge onto one neuron is of high importance for how synaptic input is integrated by single neurons. To investigate this distribution, we performed whole-cell slice-recordings of pyramidal neurons in layer 2/3 (L2/3) of mouse barrel cortex. We measured the STP responses by paired-pulse protocols for multiple synapses per neuron by minimal stimulation of single fibers at different locations in L2/3. Our intention was to measure as many single fiber inputs to a neuron as possible. In total, we recorded responses from 74 single fibers that formed synapses with 20 different neurons in 13 mice. The EPSP amplitudes of these 74 synapses had a mean of 1.23 ± 0.75mV and followed a log-normal distribution. With a paired-pulse interval of 20ms, the paired-pulse ratios (PPRs) of the recorded synapses indicated synaptic depression. The PPRs followed a normal distribution with a mean of 0.93 ± 0.20. For 8 neurons, we obtained measurements of at least 5 different synapses each. Strikingly, the PPR distributions for any of these 8 neurons was never significantly different from the overall PPR distribution in L2/3. This suggests that there is no clustering of STP values on individual pyramidal neurons in L2/3 of mouse barrel cortex.
**B11**  
Astrocytic glutamate release induces action potential-independent network-wide synchrony in hippocampal neurons

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In recent years, astrocytes have become increasingly appreciated as key modulators of neuronal activity. It is now known that these cells are capable of regulating synapse formation, plasticity and neuronal synchronization. Recent evidence also implicates astrocytes as gate-keepers of cortical network states. Proof of regulating neuronal synchronicity in the hippocampus, however, has been limited to relatively small populations of cells. We now show that, in the hippocampus, the astrocytic syncytium is capable of inducing network-wide synchronization without the need for action potentials. In acute hippocampal mouse slices, we find that the application of potassium channel antagonists induces spontaneous, large slow inward currents (SICs) throughout the entire neuronal circuit that persist in the presence of TTX. Using combined whole-cell electrophysiological recordings and neuronal calcium imaging, we observed events initiating in CA3c with those in distal CA1 following approximately 100 ms afterwards. Astrocytic imaging revealed circuit-wide calcium elevations coincident with neuronal SICs. Furthermore, pharmacological and optogenetic inhibition of glial glutamate release inhibited these events. As the astrocytic syncytium is functionally coupled via gap-junctions, with each of its cells contacting thousands of neurons, it is well poised to control large circuits with strong temporal correlation. Our work demonstrates that hippocampal astrocytes are capable of synchronizing not only neurons in local domains, but the entire Cornu Ammonis structure, lending evidence to hypotheses that astrocytes play a critical role in coordinating network events.

**B12**  
The Presynaptic Proteasome is Required for Homeostatic Recruitment of Low Release Probability Vesicles

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Robust neural function is a prerequisite for stable animal behavior. However, the molecular underpinnings of robust neural activity have remained largely elusive. Work during the last decades has revealed that synaptic function is stabilized by evolutionarily conserved homeostatic signaling systems. The Drosophila neuromuscular junction (NMJ) has emerged as a powerful model synapse to unravel the genetic basis of homeostatic regulation of neurotransmitter release. Yet it is unclear how the proteins encoded by the identified genes are regulated during homeostatic plasticity. At this synapse, the acute induction of homeostatic potentiation of release does not require protein synthesis. However, the role of local synaptic protein degradation has not been investigated yet. Here we demonstrate that homeostatic potentiation of neurotransmitter release requires synaptic proteasome function. Genetic data suggest that presynaptic, but not postsynaptic proteasome function is necessary for homeostatic modulation of release. Moreover, we show that presynaptic proteasome perturbation enhances presynaptic Ca2+ influx and the release of EGTA-sensitive, low-release probability vesicles, and that these vesicles are required for homeostatic plasticity. Interestingly, proteasome impairment does not potentiate release after loss of specific homeostatic plasticity genes, including the schizophrenia-susceptibility gene dysbindin. Together, our data suggest that the presynaptic Ubiquitin Proteasome System controls the release of low release probability vesicles during homeostatic plasticity and baseline synaptic transmission.
Homeostatic control of dopamine by astrocytes in the postnatal maturation of the prefrontal cortex

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Over the last 20 years, accumulating evidence have shown that astrocytes can influence many aspects of synaptic transmission, network activity, and cognitive functions by controlling the extracellular homeostasis of ions and neurotransmitters. However, whether and how astrocytes participate in regulating the homeostasis of dopamine (DA) has never been investigated in detail. Most interestingly, recent advances indicate that astrocytes also express proteins involved in DA uptake and metabolism such as mitochondrial monoamine oxidase B (MAOB) enzyme [Zhang et al., Neuron, 2016] and, importantly, vesicular monoamine transporter 2 (VMAT2) [Romero-Calderon et al., Plos Gen, 2008; Zhang et al., Neuron, 2016], an integral vesicular membrane protein that directly controls vesicular storage of monoamines in neurons and neurosecretory cells [Edwards et al., Neuron, 2007]. Here, we find that a subset of cortical astrocytes is crucial in maintaining an efficient DA homeostasis in the developing prefrontal cortex (PFC) through expression of VMAT2. Astrocytes start to express VMAT2 during the early stage of postnatal development preceding adolescence, i.e. when the establishment of DA connectivity in the PFC occurs. At subcellular level VMAT2 in astrocytes is responsible for sequestering DA in intracellular organelles and, thus, for regulating the amount of cytosolic DA available for metabolism through MAOB activity. By using in vivo conditional gene inactivation and viral-mediated gene replacement we also find that extracellular levels of DA in the developing PFC can be potently controlled through modulation of VMAT2 expression in astrocytes. Interestingly, we show that dysfunction of the VMAT2-dependent homeostatic control of DA by astrocytes alters synaptogenesis of pyramidal neurons in PFC and finally, prevents an efficient acquisition of behavioral and cognitive performances. Support contributed: NCCR Synapsy and NCCR TransCure to P. Bezzi

Evaluation of the receptor-mediated function of lactate in neuronal activity

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Hydroxycarboxylic acid receptor 1 (HCA1R) is a G protein coupled receptor (GPCR) for lactate initially described in the fat tissue. The recent discovery of its presence in neurons of the central nervous system, has pointed to
additional non-metabolic effects of lactate on neuronal network activity. At the functional level, 3,5-DHBA and 3-Cl-HBA, non-metabolized agonists of HCA1R, reversibly decreased by 40% spontaneous spiking activity of primary cortical neurons of wild-type mice, and 3,5-DHBA did not affect the activity of neurons prepared from HCA1R knock-out animals. Similar to what was described in fat tissue, we present evidence that HCA1R in neurons mediates its effect through the inhibition of adenylyl cyclase and PKA. These results together with the previously demonstrated sensitivity of HCA1R effects to pertussis toxin (a Gi protein deactivator), strongly indicates that HCA1R is mediating its effect on neurons through a Gi protein. A characteristic feature of GPCRs is their ability to cross-talk with other GPCRs. We found that HCAR1 cooperates with A1R and GABABR for the modulation of the neuronal network activity. Our results demonstrate the requirement of HCA1R activation for the non-metabolic effect of lactate on neuronal activity, and provide strong support for its role as modulator of the neuronal network.

**B15**

Interplay between homeostatic and non-homeostatic modulation of neurotransmitter release at the Drosophila neuromuscular junction

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While changes in synaptic transmission are crucial for learning and memory formation, uncontrolled changes may destabilize neural function and result in pathologies. It is therefore important to unravel the mechanisms that stabilize synapse function while providing synapses with the capacity for change. We here combine electrophysiological and genetic approaches at the Drosophila neuromuscular junction (NMJ) to characterize a potential interplay between homeostatic and non-homeostatic forms of synaptic plasticity. High-frequency stimulation at this synapse leads to long-term synaptic depression (LTD), a prolonged decrease in the amplitude of evoked excitatory postsynaptic potentials. We provide evidence that LTD is caused by a concomitant decrease in presynaptic release probability and readily-releasable vesicle pool size. Synaptic transmission at depressed NMJs was more sensitive to EGTA-mediated Ca2+ buffering suggesting an increased distance between presynaptic Ca2+ channels and release-ready vesicles during LTD. Interestingly, we observed an increase in mEPSP amplitude when inducing LTD at homeostatically potentiated synapses or in homeostatic plasticity mutants. Together, these data indicate that postsynaptic mechanisms counteract LTD at synapses after homeostatic challenge and at synapses that cannot undergo homeostatic potentiation of release.

**B16**

Neuronal and synaptic bases of novelty seeking

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Novelty seeking is a personality trait that influences the extent to which a person responds to novel stimuli and it is linked to the aetiology of several psychiatric disorders. Dopamine (DA) neurons within the reward circuit respond to novelty and habituate when a stimulus becomes familiar without any reinforcement. Here, using in vitro slice recordings, chemogenetic approaches and behavioral tasks in mice, we aim at identifying the neuronal and synaptic bases of novelty seeking. We found that VTA DA neuron activity is essential to express appropriate exploratory behavior in response to social, but not object, novel stimuli. Experience-dependent synaptic plasticity occurs at excitatory synapses on a rapid timescale and it is fundamental to promote specific adaptive behaviors. Using an ex vivo approach, we investigated whether acute or repeated interaction with novel stimuli induce any long-lasting form of synaptic plasticity at excitatory inputs onto DA neurons and whether any difference is observable depending on the nature of stimulus (social/object). We found that, regardless of the nature of the novel stimulus, 24 hrs after novelty exposure non-canonical GluA2-lacking AMPARs are inserted at excitatory inputs onto DA neurons. However, GluA2-lacking AMPARs are present only after repeated exposure to social stimuli and not inanimate object. Therefore, while the insertion of GluA2-lacking AMPARs is associated with the saliency of the experience, the persistence of these receptors at the synapse depends on the nature of the stimulus.
Neuropathic pain impairs spike-timing dependent long-term depression in layer 5 pyramidal neurons of the anterior cingulate cortex

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Chronic pain is caused by irreversible neuronal alterations in the pain processing system from the periphery to cortical pain processing areas. The cellular mechanisms leading to a sensitization of the pain network range from changes in cellular excitability, network restructuring to malfunction of synaptic plasticity mechanisms. It has been suggested that enhanced long-term potentiation of synaptic transmission contributes to the chronic pain state. In contrast, little is known about impact of chronic pain on long-term depression.

We investigated spike-timing dependent depression (tLTD) in the anterior cingulate cortex (ACC), a brain region involved in the emotional/affective processing of pain. Here we show that depression of synapses onto layer 5 pyramidal neurons in the ACC was abolished in adult mice when subjected to chronic constriction injury (CCI) of the sciatic nerve, an animal model for neuropathic pain.

We investigated the underlying plasticity mechanism in naïve animals and found that tLTD depended on postsynaptic calcium-influx through NMDARs, which then triggered the synthesis of nitric oxide (NO). NO acted as a retrograde messenger causing a decreased release probability. Next, we thought to identify the component of the tLTD signaling cascade that was altered in neuropathic pain. Bath application of a NO donor induced LTD in sham and CCI animals suggesting that neuropathic pain affected NO synthesis but not downstream signaling pathways. Analyzing the role of NMDARs revealed an increased NMDAR:AMPAR ratio in the CCI condition and that LTD induction was inhibited by blocking specifically NMDARs containing the GluN2B subunit. Strikingly, in the CCI condition the contribution of GluN2B to the NMDAR currents was completely lost. Our results suggest that neuropathic pain causes a switch in the NMDAR subunit composition occluding the induction of tLTD. We hypothesize that reinstating LTD in the ACC might be a potential strategy to alleviate chronic pain.

LTP in the mouse barrel cortex driven by cooperative lemniscal and paralemniscal pathway activity.

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Long-term potentiation (LTP) is thought to underlie changes in synaptic efficacy during cortical plasticity and learning. Our lab has shown in vivo that rhythmic whisker stimuli (RWS) induce synaptic LTP in layer (L) 2/3 pyramidal cells of the somatosensory barrel cortex (BC).
Whisker sensory information is primarily processed by the lemniscal pathway, which comprises neurons in the ventral posteromedial (VPM) thalamus that mainly project to BC L4 and L5B. L4 cells synapse on L2/3 pyramidal cells. Whisker stimuli also recruit activity in paralemniscal circuits, which contain projections from the posteromedial complex of the thalamus (POm) to BC L1 and L5A. Our lab has found that RWS causes a prolonged coactivity of these pathways and thereby drives LTP. However, the exact nature of the synaptic circuits that are involved remains elusive.

Here, using whole-cell patch clamp in thalamocortical slices, we found that repeated coincident pairing (RCP) of lemniscal and paralemniscal pathways by electrical stimulation of L4 and optical stimulation of channelrhodopsin-2 expressing POm inputs was sufficient to evoke LTP of the L4-to-L2/3 synapses. RCP failed to induce LTP when POm neurotransmission was suppressed using Designer Receptors Exclusively Activated by Designer Drugs (DREADD), or when NMDA receptors were blocked.

We then tested the role of GABAergic inhibition. It has previously been shown that L2/3 pyramidal dendrites are efficiently inhibited by somatostatin (SST) expressing interneurons, which in turn are inhibited by vasoactive intestinal peptide (VIP) expressing interneurons. Thus, VIP cells may disinhibit L2/3 pyramidal dendrites and thereby gate activity-dependent synaptic plasticity. In support of this we found that suppression specifically of VIP or SST interneuron activity using DREADD vectors blocked or allowed RCP- evoked LTP, respectively.

Our data identifies excitatory and disinhibitory microcircuits whose synergistic activity may facilitate sensory-driven LTP in the BC.

### C. Molecular and Subcellular Mechanisms

**C1**

**Two catalytic domain mutations of spinocerebellar ataxia type 14 negatively regulate Purkinje cell dendritic development**

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Spinocerebellar ataxia (SCA) is an autosomal dominant neurodegenerative disorder characterized by slowly progressive cerebellar dysfunction. Currently, 42 SCA types are known and unlike many SCA types which are caused by CAG repeat expansion, spinocerebellar ataxia type 14 (SCA14) is caused by missense mutations or deletions in the protein kinase C gamma (PKC-) gene. In the last decade, the different point mutations in the PKC- gene have been identified by genetic analysis but it is still not well understood how these mutations cause Purkinje cell dysfunction and death typical for SCA14. We have previously reported that mutant PKC- transgenic mice carrying the kinase domain mutation S361G from a human SCA14 allele show a severe reduction of Purkinje cell dendritic growth and development similar to be seen after pharmacological activation of PKC- kinase activity. These data raise the question whether an increased activity and the inhibition of Purkinje cell dendritic development may be also a feature of other SCA14 mutations in different domains in PKC-.

We constructed several transfection plasmids with PKC- mutations from human SCA14 and transfected them to Purkinje cells in dissociated cerebellar cultures. We found that two independent mutations in the catalytic domain of the PKC- gene caused severe inhibition of Purkinje cell dendritic development similar to the S361G mutation. On the other hand, mutations in other functional domains of PKC-, in particular in the regulatory C1b domain, didn’t show a marked effect on dendritic development when transfected to Purkinje cells in dissociated cerebellar cultures. These results indicate that there might be different pathological mechanisms of the various SCA14 mutations in the different domains of the protein and that most mutations in the catalytic domain of PKC- confer a strongly increased...
activity resulting in a severe reduction of Purkinje cell dendritic growth and development.

**C2 Exploratory RNA sequencing analysis in the dorsal and ventral hippocampus after acute stress**

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Exposure to stressful experiences can induce anxiety and neuropsychiatric disorders. It has been shown that the transcriptome of the whole hippocampus is very sensitive to acute stress challenges. Since the dorsal and ventral hippocampus are known to be functionally distinct, it remains to be determined if the two sub regions show distinct molecular responses to acute stress. Here we compare the transcriptome of the dorsal and ventral hippocampus after different acute stress treatments. Without stress exposure, we identify profound differences in the transcriptional profile between dorsal and ventral hippocampus. After stress exposure, separately analyzing dorsal and ventral hippocampus seems to reveal more information than analyzing whole hippocampal tissue. Indeed, we detect groups of stress-sensitive genes that are specific to either dorsal or ventral hippocampus, suggesting that future molecular work should treat these two sub-regions independently.

**C3 Role of neurodegeneration-associated proteins in transcellular communication**

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Most neurodegenerative disorders are caused by the accumulation of toxic proteins in characteristic brain deposits. Thus, defect in protein metabolism may contribute to the disease progression, ultimately leading to neuronal dysfunction and cell death. Our laboratory has been studying the role of the proteasomal and autophagic systems in the clearance of pathogenic proteins. Release in the extracellular space has recently gained importance as an alternative pathway to eliminate cellular proteins. Cells may secrete proteins through membrane vesicles (ectosomes, exosomes). Exosomes represent also vectors for paracrine communication between cells and play a role in the progressive spreading of disease within the brain. Open questions remain with regards to some mechanisms governing exosomal transport. Moreover, there is a need to demonstrate that soluble proteins can indeed reach the cytosol of a recipient cell.

To this end, we are currently developing reagents and tools to implement a cellular assay with a simplified read-out based on the reconstitution of protein fluorescence or enzymatic activity. As first step, we are screening multiple candidate cargo proteins commonly described as markers of exosomal cargo with the aim of identifying the most prominent positive control. The selected cargo protein will be then appropriately modified for reconstitution of GFP or of beta-galactosidase within the cytosol of the recipient cell. Furthermore, the development of a simplified assay measuring exosomal-dependent transport of soluble cytosolic proteins allows for studying and characterizing molecular drivers and regulatory mechanisms of exosomal communication as well as investigating whether the presence of neurodegeneration-associated proteins can influence...
transcellular communication in disease.

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C4 Exploratory RNA sequencing analysis in the dorsal and ventral hippocampus after acute stress

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Exposure to stressful experiences can induce anxiety and neuropsychiatric disorders. It has been shown that the transcriptome of the whole hippocampus is very sensitive to acute stress challenges. Since the dorsal and ventral hippocampus are known to be functionally distinct, it remains to be determined if the two sub-regions show distinct molecular responses to acute stress. Here we compare the transcriptome of the dorsal and ventral hippocampus after different acute stress treatments. Without stress exposure, we identify profound differences in the transcriptional profile between dorsal and ventral hippocampus. After stress exposure, separately analyzing dorsal and ventral hippocampus seems to reveal more information than analyzing whole hippocampal tissue. Indeed, we detect groups of stress-sensitive genes that are specific to either dorsal or ventral hippocampus, suggesting that future molecular work should treat these two sub-regions independently.

C5 Regulation of microRNAs by Protein Phosphatase 1 for memory formation and aging-related memory decline in mice

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Aims: Recent research has indicated that microRNAs (miRNAs) in the brain contribute to the regulation of synaptic plasticity and memory formation. We investigated if protein phosphatase 1 (PP1), a potent memory suppressor, can modulate the expression of miRNAs relevant for memory, and whether a dysregulation of PP1-dependent miRNAs is implicated in aging-related memory decline.

Methods: We conducted a deep-sequencing screen for hippocampal miRNAs using a transgenic mouse model (NIPP1 mice) with improved memory resulting from inhibition of nuclear PP1 in forebrain neurons. Several miRNAs relevant for memory formation were identified and their expression in the hippocampus was compared between young and aged mice. Analyses involving inhibition of nuclear PP1, cellular senescence, and manipulation of neurodegeneration-related proteins in mouse neuroblastoma cells were conducted.

Results: Specific miRNAs, notably miRNA cluster miR-183/96/182, are differentially expressed in the hippocampus of NIPP1 mice. The cluster shows a similar pattern of regulation in wild-type mice after training. Over-expression of the cluster in the adult mouse hippocampus enhances long-term memory whereas its knock-down impairs memory. Mechanistically, PP1 regulates the biogenesis of miR-183/96/182 in a transcription-independent manner mainly by enhancing the activity of the microprocessor complex which
increases the level of miRNAs precursors. Finally, increased nuclear PP1 activity associated with aging affects the biogenesis of these miRNAs and correlates with memory decline. Such aging-related decline be reversed by expressing miR-183/96/182 in the hippocampus.

Conclusion: We provide novel evidence that nuclear PP1 regulates the biogenesis of specific miRNAs associated with memory in mice. This regulatory pathway is likely implicated in aging-related memory decline.

C6 Different Wnt signaling pathways cooperate for commissural axon guidance

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In the chicken spinal cord, dI1 commissural neurons are a suitable model to study the role of morphogens in axon guidance. A posterior high to anterior low gradient of Shh induces Sfrp, which in turn shapes a Wnt activity gradient with opposite orientation. Wnts act as attractive guidance cues for postcrossing axons. Wnt signaling can activate independent downstream pathways: the canonical pathway and the planar cell polarity pathway. We have demonstrated that canonical receptors Lrp5/6 and -catenin are necessary for commissural axon guidance. On the other hand, planar cell polarity core molecules are also needed for this process. Our results suggest that both canonical and non-canonical pathways need to be activated for proper postcrossing axon guidance. However, the specificity of Wnt ligands to each pathway is unknown and also how these molecules are coordinated intracellularly.

C7 Synaptic vesicle exocytosis visualized by cryo-fluorescence and cryo-electron microscopy in millisecond resolution

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Exocytosis at the chemical synapse is orchestrated by a pool of vesicles tethered to the active zone plasma membrane by the SNARE fusion machinery. Upon depolarization the SNARE complex is remodeled and a hypothesized curvature step of both the active zone plasma membrane and the synaptic vesicle is induced. This curvature step would reduce the energy barrier of the two opposing membranes followed by synaptic vesicle fusion. However, to date the molecular mechanism remains elusive due to the fact that it is a process that can be as fast as 0.2 ms.

To visualize exocytosis we use isolated functional synapses (synaptosomes) rapidly plunge frozen milliseconds after depolarization. This method allows a close-to-native state preservation of the sample and an analysis of exocytosis events captured as fast as 1 ms. Synaptosomes are then analyzed by correlative cryo-fluorescence and cryo-electron microscopy followed by 3D reconstruction of the obtained data. Our data show membrane curvature events prior to fusion of the vesicle as well as some potentially short lived states between curvature and fusion and also full-collapse fusion events itself. These events could not be found in control synaptosomes.

Based on our ex vivo observations we believe that it will be possible to analyze structural changes of exocytosis and thereby unravel its underlying molecular mechanism to shed electrons on this very fast process.
RNA-binding proteins controlling spatial specificity of CNS synapse formation

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Central nervous system development requires diverse molecular mechanisms to determine the establishment of functional neuronal circuits. These mechanisms control neuronal differentiation, cell migration and polarization, axon and dendrite targeting, branching, and synaptogenesis. The question of how each neuron finds its correct synaptic partners (“synaptic specificity”) is central to the assembly of neural circuits. Equally intriguing is, at the subcellular level, what mechanisms underlie how different axonal branches can diverge to connect to different targets. Proteins with RNA binding domains emerge as promising candidates to provide such spatial specificity, due to their potential for differentially regulating gene expression by local translation in individual axon terminals. This potentially provides a neat mechanism for autonomous control of diversity and specificity of axonal branches.

To address these questions we use a set of genetic tools that allow us to label and manipulate with single neuron resolution a specific type of mechanosensory (ms) neuron in the Drosophila central nervous system (CNS). Ms neurons have three stereotypic branches with different characteristics regarding their targets, and their amount and density of pre-synapses. These characteristics make them an attractive model to study the assembly of circuits within the complexity of the CNS.

We are interested in the role of local translation in establishing branch-specific connectivity patterns. As an entry point, we aim at identifying RNA-binding proteins that are required for ms neuron wiring. One candidate recovered in a small-scale RNAi screen is Musashi (Msi), a protein with two RNA-binding domains that has been implicated in maintenance of neuronal progenitors and stem cells, as well as in some neurological disorders and memory maintenance. However, its role in neuronal wiring and developmental synaptogenesis is largely unknown. We found that Msi promotes higher-order branching and synapse formation specifically on one branch in ms neurons. Furthermore, Msi protein localizes to axon branches in the CNS.

Our findings provide a starting point to elucidate the role of local translation in conferring synaptic specificity, as well as the molecular functions and mRNA targets of Msi.

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Layer-specific sensory-motor integration in mouse barrel cortex during exploratory locomotion

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There is increasing evidence that locomotion modulates sensory processing in primary sensory cortices of mice. Here, we investigate how animal movements (running and whisking) are integrated with tactile touch stimuli in...
primary somatosensory cortex (S1) of mice during exploratory locomotion. We focus on differential processing across superficial (layer2/3) and deep (layer5) cortical layers. To mimic this exploratory locomotion behavior we developed a virtual tactile environment, in which mice can run in the dark, along a “wall”, on which textures are presented. Mice are head restrained on a treadmill and textures are presented on rotating cylinders in reach of whiskers. During behavior, we perform 2-photon calcium imaging of cortical neurons, expressing the calcium indicator R-CaMP-1.07. We found that in both superficial and deep layers, subsets of neurons show increased activity with locomotion. A larger set of neurons were responsive to initial contact of rotating textures. A major difference between layers appears to be the persistence of the response to touch such that in layer 2/3, neurons continue to respond to rotating stimuli whereas the activation of layer 5 neurons is transient and gets suppressed after the initial touch activity. These results highlight layer-specific differences in the integration of sensory-motor aspects in barrel cortex.

D2  Centromedial thalamus (CMT) control of cortical state during sleep.

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Mammalian midline thalamus consists of five nuclei of ambiguous function whose integrity is obligatory for maintenance of consciousness, cognition and sleep. Each of these functions relies on a tightly regulated UP-DOWN-states of thalamo-cortical networks. Here, we investigated the role of the midline thalamus on control of local and global cortical states during sleep. We found that CMT spiking activity is modulated across sleep states. CMT local field potentials show a phase-advancement over other midline-thalamic nuclei and cingulate cortex during the UP state of spontaneous NREM slow waves, which is consistent with a CMT-Cingulate monosynaptic pathway. We further found that optogenetic activation of CMT entrains cortical spiking activity in cingulate, parietal and occipital cortex and was accompanied by wakefulness. Interestingly, parietal and occipital entrainment occurred simultaneously, lagging behind responses observed in the cingulate. Using dual activation-silencing stimuli, we showed that spike and LFP transfer to parietal an occipital cortex, as well as wakefulness, is dependent on the dorsal thalamus. In contrast, stimulation of VB did not result in wakefulness. Collectively these results implicate the CMT as the main driver of local cortical UP-states via monosynaptic input to the cingulate. However, changes in global cortical state and wakefulness, are dependent on a functional relay located in the dorsal thalamus. These results support both a correlative and causal role of midline-thalamus in control of frontal cortical states during sleep.

D3  Modulation of oscillatory activity in the rat ventral striatum by dopaminergic signaling

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The ventral striatum (VS) is a key element in the brain circuitry controlling reward behavior and decision making, sociability, and motivation. In humans dysfunction of the VS is associated with a variety of diseases, such as depression, addiction, and schizophrenia (SZ).
The VS consists mainly of different types of GABAergic neurons, i.e. fast-spiking interneurons, and medium spiny neurons (MSNs). MSNs are inhibitory projection neurons and have been divided classically into the direct pathway made up by dopamine (DA) D1 receptor (D1R)-expressing neurons, and the indirect pathway consisting of D2 receptor (D2R)-expressing cells.

The VS receives excitatory input from cortical and limbic structures, as well as prominent DAergic input from the ventral tegmental area (VTA). Alterations in DA-mediated modulation of VS activity is thought to contribute to disease symptoms such as lack of motivation in SZ, or drug seeking in addiction.

Here we characterize oscillatory activity in the rat VS, which is dominated prominent oscillations in distinct gamma bands, as well as high frequency oscillations (HFOs). VS activity spontaneously alternates between 50 Hz- and 80- Hz gamma bursts.

Interestingly, both pharmacological activation and blockade of D1Rs with SKF81279 or SCH39166, respectively, led to strong increases in gamma activity, but in differential frequency bands. Specifically, D1R activation resulted in an increase in 80 Hz-gamma, whereas SCH39166 increased 50 Hz-gamma power. Activation of D2Rs by quinpirole led to an increase in 50 Hz-gamma power and a concomitant reduction in the mean frequency in several oscillatory bands. Currently we are investigating the effect of D2R blockade by raclopride, a widely-used antipsychotic, on VS oscillations.

In summary, we show that modulation of D1R and D2R activity reveals distinct signatures in VS oscillatory activity, which may provide a framework for the development and characterization of novel pharmacological compounds seeking to normalize VS pathways in disease.

**D4**

**The affiliation of individual cortical neurons with global cortical networks**

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The neocortex is richly interconnected, and different cortical areas exhibit shifting affiliations with one another depending on behavioral state or context. This coupling is subserved in part by the excitatory long-range projections between cortical areas. Neighboring neurons may send projections to and receive input from local and distant areas. In addition to their heterogeneous connectivity, cortical neurons fall along a spectrum of engagement with shared local activity—while some are preferentially co-active with their neighbors, others are not functionally coupled to the local network. This response heterogeneity might reflect the variety of global influences on individual cells. We therefore undertook to map the relationship between the activity of individual neurons and the activity in distant areas, and sought to relate these functional maps to the strength of a cell's coupling to shared local activity.

In order to probe the affiliation of individual cells with distant networks, we recorded extracellularly from single units in visual cortex while simultaneously imaging cortex-wide activity in transgenic mice expressing the calcium indicator GCamp6s in CaMKII+ neurons. We made maps of the strength of correlation between individual units and various cortical areas. While many neurons shared similar cortex-wide correlation maps, a small proportion had unique affiliations, and these were often the cells most negatively coupled to local activity. Given that activity in primary sensory cortices not only reflects the occurrence of a sensory stimulus, but information about the animal's behavioral state and stimulus context, this method might be used in behaving animals to relate dynamic long range influences on the spiking of individual cortical neurons during various behaviors.
Synaptic organization of visual space in primary visual cortex

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How a sensory stimulus is processed and perceived depends on the surrounding sensory scene. In the visual cortex, contextual signals can be conveyed by an extensive network of intra- and inter-areal excitatory connections that link neurons representing stimulus features separated in visual space. However, the connectional logic of visual contextual inputs remains unknown; it is not clear what information individual neurons receive from different parts of visual field, nor how this input relates to the visual features a neuron encodes, defined by its spatial receptive field. We determined the organisation of excitatory synaptic inputs responding to different locations in the visual scene by mapping spatial receptive fields in dendritic spines of mouse visual cortex neurons using two-photon calcium imaging. We found that neurons received functionally diverse inputs from extended regions of visual space. Inputs representing similar visual features from the same location in visual space were more likely to cluster on neighbouring spines. Inputs from visual field regions beyond the postsynaptic neuron’s receptive field often synapsed on higher-order dendritic branches. These putative long-range inputs were more frequent and more likely to share the preference for oriented edges with the postsynaptic neuron when the input’s receptive field was spatially displaced along the axis of the postsynaptic neuron’s receptive field orientation. Therefore the connectivity between neurons with displaced receptive fields obeys a specific rule, whereby they connect preferentially when their receptive fields are co-oriented and co-axially aligned. This organization of synaptic connectivity is ideally suited for amplification of elongated edges, which are enriched in the visual environment, and thus provides a potential substrate for contour integration and object grouping.

Optogenetic interrogation of distinct and complementary nigral sub-circuits that shape movement

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Motor Behavior stands at the core of every mammalian organism’s survival and evolvement within its environment. The Substantia Nigra Pars Reticulata (SNr) has long been identified as the prime output nucleus of the Basal Ganglia, an ensemble of brain structures that governs motor behavior. The SNr is commonly regarded as GABAergic and homogenous. Its activity patterns have been correlated with different aspects of locomotion such as sensory input, movement planning, execution and interruption. Such versatile function suggests a more complex organization of the SNr than has been thought so far. Using a combination of anatomical and functional techniques, we identify two marginally overlapping sub-populations of GABAergic neurons that are embedded within separate circuits, execute different functions, and act complementarily to sculpt locomotion. We provide fundamental understanding of basic SNr circuitry and function with a cell-type specific resolution. This represents a critical step in refining our knowledge in the cellular, synaptic and circuit bases of motor-related behaviors.
Exploring the “Zone of Uncertainty”

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Dopamine (DA) is a diffuse neuromodulator that acts upon large areas of the brain from small, scattered, but densely populated clusters of neurons, playing a major role in motor control, motivated behaviors, arousal, and executive functions. In the last half of a century, more than a handful of these clusters have been identified. Of these, the midbrain dopaminergic (DAergic) clusters, notably ones of the Ventral Tegmental Area (A9) involved in motivated behaviors and the Substantia Nigra pars Compacta (A10) involved in motor control, are the most studied. However, other clusters, such as the A13 DAergic cell group, have been largely overlooked.

Located in the rostral portion of the Zona Incerta (rZI), the A13 is particularly peculiar. The A13 DAergic neurons have been shown to express the machinery both to produce and package DA (tyrosine hydroxylase TH and vesicular monoamine transporter VMAT2, respectively). However, they completely lack the dopamine transporter (DAT), the pump responsible in the reuptake of DA. In addition to its unique molecular identity, little is known about its functional role. Early studies implicated the A13 with ingestive behaviors, however, with the lack of specificity, the crude nature of the manipulations, and its proximity to the lateral hypothalamic area, these findings must be taken with a grain of salt.

With the advancement in modern techniques, we take a comprehensive approach to investigate the A13 DAergic cell group on several levels, with the aims of better understanding this unique yet mysterious region. Using fluorescently labeled antibodies and mRNA probes, we investigate the cell identities within the rZI by examining the different combinations of the co-expression of the machineries of the DAergic (VMAT, DAT), GABAergic (VGAT, GAD), and glutamatergic (vesicular glutamate transporter VGlut2) systems. With the unspecific expression of fluorescent proteins and retrograde tracers in the rZI, we investigate the outputs and inputs to rZI, respectively. Furthermore, in conjunction with cell type specific Cre-lines, we characterize that of the specific cell populations within this region. Lastly, with whole cell patch clamp recordings, we assess the electrophysiological properties of the A13 DAergic neurons, another measure of cell identity, as well as to gain further insight on their firing property, excitability, and response to changes in the local environment. Together, our three-pronged approaches would provide early and direct insight onto the mysterious A13 DAergic neurons, paving the way for future investigations into their functional relevance.

Automated dense collection of ultrathin sections directly onto silicon wafers

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Silicon wafers constitute ideal substrates for carrying ultrathin biological tissue sections for subsequent imaging using either array tomography, correlative array tomography, or multibeam scanning electron microscopy technology. We developed a method for the automated collection of hundreds of consecutive ultrathin sections directly onto silicon wafers. Hundreds of floating ultrathin sections carrying magnetic material are densely...
accumulated with remote magnetic actuation at the water surface in a custom diamond knife bath. The sections are
subsequently deposited directly onto a previously immersed silicon wafer onto which we routinely collect about 1000 sections of
about 1 mm² occupying as little space as about 25 cm² (40% wafer covering density). The cutting order of the sections is
retrieved either using light or electron microscopic imagery by solving a global optimization problem.
We are currently scaling up our approach to the collection of several thousands of sections onto a single large silicon wafer. We
hope that our technology will help accelerate volumetric structural research efforts such as connectomics.

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D9  
Reconstruction of neuronal activity and connectivity patterns in the zebrafish olfactory bulb

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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 interneurons (INs). This reorganization results in multiple computations including a decorrelation of activity patterns
across the output neurons, the mitral cells (MCs). To understand the mechanistic basis of these computations it is essential to
analyze the relationship between function and structure of the underlying circuit. We combined in vivo multiphoton calcium
imaging with dense circuit reconstruction from serial block-face electron microscopy (SBEM) stacks of the larval zebrafish OB
(4.5 days post fertilization). To address bottlenecks in the workflow of this emerging methodology we developed a procedure for
conductive sample embedding, a pipeline for high-throughput image annotation and a workflow to correlate SBEM stacks with
light microscopy data of the same specimen. We reconstructed all neurons (n > 1,000) in the olfactory bulb of a zebrafish larva
with high accuracy and annotated > 300,000 synapses of different neuron types. We identified new, rare cell types and found
that the IN network organization is governed by glomerular identity. For > 80% of the reconstructed neurons we were able to
map neuronal activity that was measured in the same specimen prior to electron microscopy (EM). Decorrelation of activity
patterns elicited by similar natural odors was present already before the emergence of granule cells, but is mediated by specific
inter-glomerular IN projections. These results provide strong evidence that the topology of IN networks in the OB determines
circuit function, and that the network is optimized, presumably by evolution, to process representations of natural odors.

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D10  
Oxytocin receptor signaling in the prefrontal cortex modulates the inhibition of fear responses by the amygdala.

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The projections from different areas in the medial prefrontal cortex (mPFC) to the amygdala modulate fear expression and
extinction. The prelimbic cortex (PL) projects to the basolateral area of the amygdala (BLA) and facilitates fear expression;
wheras, the infralimbic cortex (IL) projects to the intercalated cell masses (ITC) and promotes fear extinction. Here, we
hypothesized that the oxytocin receptor (OTR) modulates these two pathways.
In the mPFC, OTR have been found in somatostatin positive cells, a type of interneurons (INs) that inhibit the dendrites of pyramidal neurons, but also the parvalbumin positive neurons. Thus, the OTR signalling could be involved in an inhibitory/desinhibitory circuit within the mPFC, regulating the projections to the amygdala.

We traced the projections from the mPFC (PL/IL) to amygdala’s subnuclei (BLA/ITC) by retrograde labelling; this tracing technique was coupled with patch clamp recordings, in order to identify the sensitivity of amygdala projecting neurons in the mPFC to oxytocin.

OTR activation in fluorescent cells within the PL (L5) increases IPSC frequency. This suggests that the OTR signalling could inhibit the projections from PL to BLA, and therefore, reduce fear expression.

Moreover, in vivo inactivation of OTR in the PL during fear conditioned avoidance learning, increases fear expression measured as freezing behaviour and the latency to avoid the footstock after conditioning.

Taken together, these results support the idea that the OTR promotes the inhibition of pyramidal neurons in the PL, consequently, the fear projections to the amygdala.

D11 LOW FREQUENCY MICROSTIMULATION IS LOCALLY EXCITATORY IN PATIENTS WITH EPILEPSY

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Deep brain stimulation (DBS) could become a palliative treatment for patients with drug-resistant epilepsy for whom surgery cannot be proposed. The objective of this study was to perform microstimulation to measure the effects of DBS in epilepsy locally at the level of a few neurons, with microelectrode recordings, for the first time in patients with epilepsy.

Microelectrode recordings were performed before, during and after microstimulation in seven patients with refractory epilepsy. Neuronal spikes were successfully extracted from multi-unit recordings with clustering in 4/5 patients during hippocampal and in 1/2 patient during cortical dysplasia microstimulation (1 Hz, charge-balanced biphasic waveform, 60 s/ph, 25 A).

The firing rate increased in 4/6 periods of microstimulation and remained significantly higher than before in 5/6 periods. Low-frequency microstimulation was hence sufficient to induce neuronal excitation lasting beyond the stimulation period. No inhibition was observed.

This report presents the first evidence that microstimulation performed in epileptic patients produced locally neuronal excitation. Hence neuronal excitation is shown here as the local mechanism of action of DBS. This local excitation is in agreement with epileptogenic effects of low-frequency hippocampal macrostimulation.
An open-source framework for scalable analysis of brain imaging data

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Over the last decade, advanced imaging techniques such as two-photon or light-sheet microscopy have become an important part of the neuroscience toolkit. However, the management and analysis of the huge amount of data produced by these techniques pose significant challenges for many labs. In particular, conventional approaches to data analysis (single workstation, custom-written scripts) scale poorly to datasets comprising hundreds of gigabytes or terabytes. These problems can be addressed by recently developed Big Data computing frameworks, notably Apache Spark [1], which promise easy-to-use, scalable data analysis on commercial cloud computing platforms. While these systems are powerful and their applicability to neuroscience has been demonstrated [2], the technical know-how required for implementing workflows based on Spark is still beyond what is available in most neuroscience labs. Moreover, the use of commercial cloud computing platforms may raise concerns regarding cost control and privacy. To address these issues, we have implemented a framework for scalable and easy-to-use analysis of brain imaging datasets, based on deploying Apache Spark in an open-source cloud computing environment (OpenStack). The workflow encompasses import of raw data (stored on OpenStack Swift), a customisable preprocessing pipeline, data visualisation as well as higher-level analytics. User interaction is achieved simply with a web browser based on Jupyter notebooks. The whole setup is easily configurable and transferable between cluster instances. We apply our framework to the analysis of widefield calcium imaging data acquired in mice performing a texture-discrimination task. We found that preprocessing of full frame movies (512×512 pixels, 20 Hz frame rate) is considerably faster with our approach, compared to similar analysis on stand-alone machines, and scales well with the number of machines/cores in the cluster. More complex analyses, such as sliding-window correlation and regression, which are computationally too costly to run pixel-wise on a single machine, become possible with the distributed approach presented here. Our open-source framework is freely available to the community and is expected to become a useful tool for the analysis of similar datasets acquired in different laboratories.

References:

Identification of novel afferents to the thalamic reticular nucleus.

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The thalamic reticular nucleus (TRN) is a key player in sleep spindle generation and a cornerstone of attentional mechanisms. It modulates state-dependent interactions between thalamic circuits and sensory cortices.
Far from being a homogenous GABAergic nucleus, accumulating evidence suggest considerable heterogeneity in the neurochemical nature and the synaptic connectivity of the TRN. The anterior portion of the TRN is connected to limbic structures, yet little is known about its role in thalamocortical communication. The aim of this project is to identify novel afferents to the TRN to bring insight into unknown functions of this strategically positioned nucleus. We combined anatomical techniques using immunostaining and tracers with in vitro/in vivo electrophysiology and optogenetic stimulation. Our results show that the anterior TRN receives a monosynaptic glutamatergic input from the post subicular region, which show little short-term depression. Subicular projections induce also direct excitation and feedforward inhibition of anterior thalamic neurons. These data suggest a role of the TRN in the modulation of the head-direction signal that is essential for the spatial navigation system.

**D14** Illuminating the function of inhibitory microcircuits in the zebrafish homolog of olfactory cortex

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The brain creates dynamic representations of the sensory environment by extracting stimulus features at early processing stages and synthesizing more abstract object representations in higher brain areas. We dissect the function of neuronal microcircuits in a higher olfactory brain area to identify elementary computations of basic cortical circuits and to analyze the underlying cellular mechanisms. We use a combination of genetic, electrophysiological and optical approaches to visualize and manipulate different types of interneurons (INs) in the posterior zone of the dorsal telencephalon (Dp) of adult zebrafish. This brain area is homologous to olfactory cortex in mammals and assumed to be involved in olfactory object representations and associative memory. We identified two types of inhibitory INs that have similar electrophysiological properties but are differently connected to other neurons in Dp. Both IN types provide divisive inhibition, a particularly important form of inhibition in auto-associative memory networks, which has so far not been observed in olfactory cortex. In addition, we observe that Dp interneurons are involved in other functions, including separation of similar odor representations, representation of odor objects, and in regulation of neuronal plasticity.

**D15** Neuronal circuitry for conditioned fear in the basolateral amygdala.

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Fear and anxiety are emotions experienced by all individuals and can serve as an adaptive process in shaping decisions and behaviors related to survival of an organism. However when fear becomes pathological, it forms the basis of a variety of potentially devastating anxiety disorders. Numerous studies have provided evidence that the function of the amygdala may be dysregulated in emotional disorders such as anxiety and depression.
One region of particular interest is the basolateral amygdala (BLA), which integrates information from sensory structures and other higher brain areas including the hippocampus and the medial prefrontal cortex. Using a combination of optogenetic, anatomical and imaging approaches, we identify and dissect the BLA circuitry which is necessary for the acquisition and expression of conditioned fear responses by linking sensory input to motor output.

### D16 Amygdala in social behavior

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Social behaviors encompass a complex set of conducts, which are impaired in several psychiatric disorders such as depression, autism spectrum disorder (ASD), schizophrenia and social anxiety disorder. Many efforts have been dedicated to understand social behavior, however the underlying neuronal circuits are poorly understood. A large body of research indicates that the amygdala is a key brain structure for emotional processing and memory, in particular fear learning. Although the amygdala has so far been mostly investigated in the context of fear responses, there are several studies implicating this brain area as an important structure involved in patients with ASD. Recently, some studies revealed a direct role of the amygdala during social interaction. Our aim is to dissect the contribution of defined amygdala cell types and circuits to social behavior. To this end, we employ a combination of cell-type specific targeting, single unit recordings and imaging techniques in freely behaving mice to determine the activity and causal involvement of defined amygdala circuits and projections during social interaction.

### D17 Corticobulbar projections change according to motor pathology in macaque monkeys

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The corticospinal and corticobulbar projections together with brainstem descending systems, such as the reticulospinal tact, ensure the control of voluntary movements via direct or indirect commands sent to spinal motoneurons. The aim of the present study was to investigate the corticobulbar projections from distinct motor cortical areas onto different nuclei of the reticular formation after 3 types of lesion/pathology of the central nervous system. The anterograde tracer BDA was injected in either the premotor cortex (PM) or in the primary motor cortex (M1) to label corticobulbar axonal and boutons terminaux and en passant in the Ponto-Medullary Reticular Formation (PMRF). The boutons in PMRF were quantified and normalized with respect to the number of corticospinal labelled axons.

In intact animals (n=7) the corticobulbar projections differ according to the motor cortical area of origin: PM and SMA send strong projections mainly ipsilaterally, whereas from M1 projections are less dense and mainly contralateral. After M1 cortical lesion (hand area) corticobulbar projections from PM were strongly reduced but remained mainly ipsilateral (n=4 monkeys). In contrast, the corticobulbar projection from M1 was decreased following opposite hemisection of the cervical cord (C7 level; n=4 monkeys). Finally in parkinsonian monkeys
(n=4), the corticobulbar projection from PM was reduced whereas that from M1 was unaffected. In conclusion, depending on the lesion type, connections from several motor areas rearrange differently to compensate the loss of manual dexterity.

D18  
Different modes of visual integration in the lateral geniculate nucleus revealed by single-cell-initiated transsynaptic tracing

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The thalamus receives sensory input from different circuits in the periphery. How these sensory channels are integrated at the level of single thalamic cells is not well understood. We performed targeted single cell-initiated transsynaptic tracing to label the retinal ganglion cells that provide input to individual principal cells in the mouse lateral geniculate nucleus (LGN). We identified three modes of sensory integration by single LGN cells. In the first, 1-5 ganglion cells of mostly the same type converged from one eye, indicating a relay mode. In the second, 6-36 ganglion cells of different types converged from one eye, revealing a combination mode. In the third, up to 91 ganglion cells converged from both eyes, revealing a binocular combination mode in which functionally specialized ipsilateral inputs joined broadly distributed contralateral inputs. Thus the LGN employs at least three modes of visual input integration, each exhibiting different degrees of specialization.

D19  
The role of different motor cortex subregions in goal directed action.

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Cortical motor areas consist of several interconnected subregions which are thought to play different roles in specific aspects of voluntary arm movements in primates. In rodents, two major areas have been described based on anatomy and microstimulation: a caudal forelimb area (CFA) and a rostral forelimb area (RFA). Their relative functional contribution to goal directed action is not clear. To elucidate the role of CFA and RFA, we developed a cue guided forelimb based joystick task for head restrained mice and performed optogenetic inactivation during different phases of the task. Mice were trained to discriminate between two vibrotactile stimuli and report their answer by pushing or pulling a joystick after a delay period. Correct answers were rewarded with water. All mice learned the task in 4 to 5 weeks. Forelimb movements and other motor output variables were tracked over hundreds of trials with an automated behavioral control system. Using an optogenetic laser scanning method to rapidly target different locations through the thinned skull, we found that inactivating either of the two areas impaired the performance at several levels, while inactivating surrounding regions didn’t affect the behavior. The ability to choose the appropriate movement was significantly affected when inactivating either area during the sensory and delay period, whereas the movement dynamics were only perturbed when cortex was inactivated during the response period and the effects were restricted to the CFA. In contrast to single area inactivation, the combining areas caused robust perturbation of both choice and motor variables, suggesting the existence of distributed and redundant representations of choice and execution across the different motor areas.
D20  GRP neurons in itch processing circuits of the spinal cord

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Itch, also known as pruritus, is an irritating cutaneous sensation that induces a scratch reflex. Itch has evolved to detect the presence and consequently to promote the removal of harmful agents. However, in several cutaneous and systemic diseases, itch can also become chronic, thus severely affecting the quality of life. Yet, the mechanisms that drive itch sensations are not fully understood.

Previous studies have shown that spinal neurons that express gastrin-releasing peptide receptor (GRPR) are required specifically for chemically induced pruritic behaviors. Our study aims to better understand the neural circuit that provides input to GRPR neurons. To this end, we have characterized and manipulated neurons in which Cre is expressed under the control of the GRP gene (gastrin releasing peptide), the gene that codes for the GRPR ligand. Behavioral analysis of mice after ablating GRP+ neurons showed specifically reduced itch responses to chloroquine, histamine and serotonin. Conversely, activation of GRP+ cells showed and increased spontaneous and pruritogen-induced scratching behavior. Responses to painful thermal and mechanical stimuli were unaffected by the loss or activation of GRP+ neurons. Taken together, our results indicate a specific role of GRP+ neurons in spinal itch processing circuits.

D21  Modulation of sensory processing by direct descending projections from the somatosensory cortex to the spinal dorsal horn

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Noxious stimuli are sensed by specialized nociceptors of the peripheral nervous system. The information is then integrated in the spinal cord dorsal horn, which contains many interneurons and projection neurons sending axons to the brain. Additionally, supraspinal structures in the brain send axons to the spinal cord that contribute to gating and integration of the information coming in from the periphery. In many pathologies this processing can be altered, leading to hyperalgesia and allodynia. We have identified a population of pyramidal neurons in the somatosensory cortex that projects directly to the dorsal horn of the spinal cord. In order to identify the connectivity and function of these neurons, we use genetically modified mice expressing recombinases (CRE and/or DRE) under the control of neuron type-specific promoters. In combination with the use of reporter lines and viruses harbouring recombination-dependent transgenes, these mice allow identification, manipulation, and tracing of neurons and circuits involved in pain processing. More precisely, the injection of CRE-dependent AAVs encoding fluorescent proteins has lead us to identify direct projections from the sensory cortex to the spinal cord in mice expressing the CRE recombinase under the CCK promoter. The main termination area is located in the laminae III and IV of the dorsal horn. Anterograde tracing with Wheat
germ agglutinin (WGA) revealed that about 60% of the spinal interneurons contacted by these corticospinal fibers are inhibitory. Additionally, we use adeno-associated viruses (AAVs) encoding DREADDs (Designer Receptors Exclusively Activated by Designer Drugs) or ChR2 to activate or silence neurons. Activation of cortical neurons using hM3Dq lead to a decreased sensitivity to painful stimuli and reduced avoidance of the hot chamber in a thermal place preference test. Neurochemical, morphological and functional analysis of dorsal horn circuitry, together with behavioral examination of the mice will allow to decipher neuronal players of pain processing and mechanisms of hypersensitivity.

**D22**  
**A cortico-thalamic-hippocampal circuit for remote fear memory attenuation**

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The experience of strong traumata can lead to the formation of over-enduring fear memories that risk to degenerate into a pathological state known as post traumatic stress disorder (PTSD). When recalled, previously acquired memories can enter a labile state where new information can be incorporated. This memory update process forms the basis of the most successful treatments for PTSD, where subjects are repeatedly exposed to the trauma-inducing stimulus in a safe environment, resulting in an attenuation of the fearful component of trauma-related memories. Nevertheless, such extinction paradigms are only effective if administered shortly after the traumatic experience and are less and less effective as the fearful memories become remote.

The recall of recently acquired fearful memories is known to be dependent on the hippocampus, whereas remote memory storage relies more on higher cortical areas such as medial prefrontal cortex. Nevertheless, we hypothesize that, hippocampal reactivation is necessary for remote memory update. In particular, we hypothesize that a bisynaptic cortico-thalamic-hippocampal circuit, involving the anterior cingulate cortex, the nucleus reuniens of the thalamus, and hippocampal area CA1, is critically involved in this process. To test this hypothesis, we will take advantage of a recently developed inducible double transgenic mouse line allowing for the specific tagging of active cell populations combined with viral based tracing and neural activity manipulation technologies. These state-of-the-art tools will allow us to identify the neuronal population recruited at remote memory recall and to analyze their specific morphological, electrophysiological and transcriptional changes upon extinction. Moreover, we will determine the connectivity of this neuronal population using a pseudotyped rabies virus-based retrograde tracing method. Lastly, we will assess the causal role of this cortico-thalamic-hippocampal circuit in the efficient extinction of remote traumatic memories by combining retrogradely spreading viruses with inducible chemogenetic neural activity manipulation tools.

**D23**  
**Probing cortical function with neuroprosthetic learning**

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Goal-directed movements are guided by ongoing sensory feedback from the displacement being produced. Here we asked if both the motor periphery and sensory organs can be bypassed by creating an artificial sensorimotor association directly in the cortex. Simultaneous two-photon imaging and real-time optogenetic stimulation was used to train mice to activate a single neuron in L2/3 of motor cortex (M1) to obtain rewards,
while continuous feedback of its activity level was provided by proportionally stimulating somatosensory cortex (S1). This artificial signal was necessary to rapidly learn to increase the conditioned M1 activity, detect correct performance and maintain the learned behavior. Population imaging of M1 cells revealed that the learning-related activity changes were specific to the conditioned neuron and did not entrain its non-conditioned L2/3 neighbours. Our findings demonstrate the capacity of animals to use an artificially-induced cortical channel in a behaviorally relevant way and reveal the remarkable speed and specificity at which this can occur. This “in-cerebro” paradigm can potentially substitute for natural behavior and facilitate dissecting neural circuits underlying sensorimotor learning. We have furthermore used this system to examine how pre-existing functional representations in mouse forepaw S1 and M1 are modified by imposing an artificial mapping between neural activities in the two areas.

D24 Balance and imbalance of input currents in neurons of the zebrafish olfactory cortex homolog

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Neurons receive excitatory and inhibitory inputs that, together with passive and active properties of the cell, determine when it fires or not. We investigated two important properties of these input currents, tuning and timing, in the zebrafish homolog of olfactory cortex, Dp, by recording input currents for multiple odor stimuli from >150 neurons using whole-cell voltage clamp in an ex vivo-preparation of the intact adult zebrafish brain. In a sub-region of Dp that is probably homolog to piriform cortex (pDp), we found large transient responses, both excitatory and inhibitory. Inhibition and excitation showed similar tuning strength and tuning width, arguing against the idea of systematically broader inhibition. Interestingly, we also observed significant co-tuning of excitation and inhibition. Therefore, inhibition does not sharpen, but rather slightly broaden the tuning curve of the neuron’s resulting output, the membrane potential. Next, we investigated the timing of those currents and found that, on average, inhibition is slightly more prominent in the early and excitation slightly more dominant in the late phase of the transient responses in pDp (the transient amounts to a total of ca. 1 sec). To understand how excitation and inhibition are coordinated on a much faster timescale, we used the prominent 25 Hz oscillations of local field potentials recorded in the olfactory bulb as an external reference clock to determine the relative timing of inhibitory and excitatory currents. This analysis showed that excitation and inhibition are closely time-locked on a millisecond-timescale (with inhibition delayed by 3.0 ± 0.3 ms). Altogether, we found that pDp neurons live in a state of balanced excitation and inhibition during this transient odor response phase. The idea of a balanced state is supported by the fact that the membrane resistance decreases during that phase to 1/3 of its normal value (1). This balance is maintained not only on a coarse timescale, but very precisely in time, indicating a “tightly balanced state” (2). Ultimately, this balance keeps the neuron in a strained balance just below firing threshold. At this point, the input-output-non-linearity of the neuron is maximal (3), providing the optimal working point for processes that are designed to shift this balance, e.g. neuromodulation or LTP. Interestingly, we see this balance in pDp, but not in other parts of Dp. For example, the anterior-most neurons of Dp exhibit late and long-lasting (>10 sec) non-balanced responses to odorants, allowing a glimpse on the diversity of mechanisms that the brain uses to process information.

In primary visual cortex (V1), a subset of neurons responds when a particular stimulus is encountered in a certain location in visual space. This activity can be modeled using a visual receptive field. In addition to visually driven activity, there are neurons in V1 that integrate visual and motor-related input to signal a mismatch between actual and predicted visual feedback. However, it is unclear whether such neurons can detect mismatch events in local regions of visual space, as would be generated by an externally moving object during self-motion. By locally perturbing self-generated visual flow as mice navigated a virtual-reality tunnel, we could show that neurons in V1 layer 2/3 signal mismatch between actual and predicted visual flow in spatially restricted regions of visual space. Such mismatch receptive fields were aligned to the retinotopic map of V1 and were similar in size to visual receptive fields. Thus, neurons with mismatch receptive fields signal local deviations of actual visual flow from visual flow predicted based on self-motion and could therefore underlie the detection of objects moving relative to the visual flow caused by self-motion.

It is still unclear how predictions of visual flow are generated. One possible source of predictive input to layer 2/3 is layer 5, which is densely connected with layer 2/3. We test this hypothesis by optogenetically manipulating layer 5 processes while simultaneously recording from layer 2/3 during perturbations of self-generated visual flow.
the specific tagging of active cell populations (TRAP line, Guenther et al. 2013) combined with virus-based tracing and neural activity manipulation technologies. These state-of-the-art tools will allow us first, to identify the neuronal population recruited at remote memory recall and to analyze their specific morphological, electrophysiological and transcriptional changes upon extinction; second, to determine the connectivity of this neuronal population using a pseudotyped rabies virus-based retrograde tracing method; and third, to assess a causal role of this cortico-thalamic-hippocampal circuit in efficient remote memory extinction by combining retrogradely spreading viruses with inducible chemogenetic tools.

D27 Synaptic organization of visual space in primary visual cortex

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How a sensory stimulus is processed and perceived depends on the surrounding sensory scene. In the visual cortex, contextual signals can be conveyed by an extensive network of intra- and inter-areal excitatory connections that link neurons representing stimulus features separated in visual space. However, the connectional logic of visual contextual inputs remains unknown; it is not clear what information individual neurons receive from different parts of visual field, nor how this input relates to the visual features a neuron encodes, defined by its spatial receptive field. We determined the organisation of excitatory synaptic inputs responding to different locations in the visual scene by mapping spatial receptive fields in dendritic spines of mouse visual cortex neurons using two-photon calcium imaging. We found that neurons received functionally diverse inputs from extended regions of visual space. Inputs representing similar visual features from the same location in visual space were more likely to cluster on neighbouring spines. Inputs from visual field regions beyond the postsynaptic neuron’s receptive field often synapsed on higher-order dendritic branches. These putative long-range inputs were more frequent and more likely to share the preference for oriented edges with the postsynaptic neuron when the input’s receptive field was spatially displaced along the axis of the postsynaptic neuron’s receptive field orientation. Therefore the connectivity between neurons with displaced receptive fields obeys a specific rule, whereby they connect preferentially when their receptive fields are co-oriented and co-axially aligned. This organization of synaptic connectivity is ideally suited for amplification of elongated edges, which are enriched in the visual environment, and thus provides a potential substrate for contour integration and object grouping.

D28 Clock circuits regulate daily sleep-wake cycles

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Daily rhythms in behaviour and physiology are controlled by internal circadian clocks. These allow organisms to anticipate daily environmental changes and prepare accordingly. Mice are nocturnal, and at night display two peaks of running wheel activity separated by a distinct siesta. The first peak of running wheel activity starts before the lights go off at dusk, whilst the second peak occurs before the lights come on at dawn. Thus these peaks are anticipatory, and controlled by the clock of the SCN. Using targeted manipulations of neuronal activity, we dissect how different groups of SCN clock neurons work together to regulate these daily sleep-wake
D29 System-level readout of cell-type perturbation reveals generic and circuit-specific functions of retinal horizontal cells

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Computations in the brain are performed by neural circuits that consist of many distinct elements. The retina, which converts incoming visual signals into parallel and unique output channels, is an ideal system to study how neural circuits composed of distinct cells types implement specific neural computations. Here we performed a system-level analysis of the retinal output while perturbing a genetically defined circuit element. Recording from > 30 000 retinal ganglion cells using microelectrode arrays, we found that chemogenetic perturbation of retinal horizontal cells, an interneuron type providing negative feedback to photoreceptors, led to an unexpected diverse set of effects. We demonstrate that horizontal cell feedback can both reduce and boost the responses of ON and OFF ganglion cells. Moreover, horizontal cell feedback acts on ganglion cells at different time periods of the response. Independent of the polarity of the cell and the analyzed response time period, horizontal cell perturbation led to an additive gain modulation in ganglion cells with boosted responses, but a divisive gain modulation in cells with decreased responses. In addition, we show that horizontal cell feedback is required to release the ON pathway from saturation after light increments, but only plays a minor role in the generation of ganglion cell receptive field surrounds. Functional classification of ganglion cells, based on responses to a stimulus mimicking the statistics of natural scenes, revealed that perturbation-induced effects acting on the early response period were generic, while effects acting on the late response period depended on the functional ganglion cell type. Finally, we performed whole-cell two-photon targeted patch-clamp recordings to pinpoint the circuit mechanism of an unforeseen perturbation-induced effect, the decrease of the ON rebound response in OFF cells, to a prolonged ON inhibitory input. Together, this study presents an efficient method to screen retinal output at a system-level with functional cell-type resolution and a novel way to reversibly interact with horizontal cell feedback, suggesting diverse computational roles for horizontal cells in vision.

D30 Disinhibitory amygdala microcircuits for aversive learning

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The basolateral amygdala (BLA) is an entry site for sensory information to the amygdalar complex, and local plasticity in the BLA is considered to be crucial for learning of conditioned fear responses. BLA principal neurons are under strong control of different subtypes of inhibitory interneurons. However, how each individual population of BLA interneurons contributes to sensory processing and fear learning is still poorly understood. Using a deep brain calcium imaging approach in freely behaving mice, we aim to understand how different interneuron subtypes contribute to fear learning. Imaging of identified BLA interneuron populations is achieved...
by viral transfer of genetically encoded calcium sensors, implantation of gradient index (GRIN) lenses and head-mounting of an ultra-light miniature microscope (nVista HD, Inscopix). We further apply novel intersectional viral tools and optogenetic approaches to analyse how different interneuron subgroups interact with each other, and how this disinhibitory interplay could affect plastic changes of BLA principal neurons and thus gate memory formation.

D31 Structure and function of the recurrent circuits involving layer 6 in cat visual cortex

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For cat primary visual cortex (V1), the local excitatory circuit has been described as a simple loop between layers, in which thalamic input to layer 4 is transmitted via layer 2/3 and 5 to layer 6, which projects back to layer 4 and the thalamus (e.g. Gilbert CD., Ann. Rev. Neurosci., 1983). However, a quantitative analysis has revealed that layer 5 provides only a small fraction of the total input to layer 6 (Binzegger T. et al., J. Neurosci., 2004), leaving the origin of most of the excitatory input to layer 6 unknown. By injecting a retrograde tracer selectively into layer 6 of cat V1, we found a previously unknown source of input to layer 6 from an extensive band of pyramidal cells lying around the layer 3/4 border. This new ‘inner loop’ between superficial layers and layer 6 is consistent with the similar receptive field sizes found in these layers (Grieve KL. and Sillito AM., J. Neurosci., 1995) and implies that layer 6 can provide fast feedback to layer 4 in addition to the slower layer 5 route.

Evidence of the functional influence of layer 6 on layer 4 of cat V1 is conflicting: Bolz and Gilbert (Bolz J. and Gilbert CD., Nat., 1986) found it to be inhibitory, but Grieve and Sillito (Grieve KL. and Sillito AM., Exp. Brain Res., 1991) found it to be excitatory. In an attempt to resolve this paradox, we measured the contrast response function (CRF) of neurons in layer 4 while pharmacologically inactivating layer 6. Two thirds of the units were facilitated during local layer 6 inactivation, but the remaining third showed diminished responses. While this decrease in gain can be explained with the inactivation of direct excitatory-excitatory projections (Ahmed B. et al., J. Comp. Neurol., 1994), the dominant disinhibition we observed suggests that layer 6 can exert a far larger range of gain control of layer 4 than previous studies indicated.

D32 Reaching for water: a novel cortex dependent forelimb task for mice

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Cutting edge genetic and optical tools to study neural circuits in the mouse only gain their full potential in combination with well-controlled behavioral paradigms. In rodent motor research, the “reach-to-grasp” behavior has proven to be a powerful paradigm because it closely resembles that of primates and it has been well characterized in the context of stroke and Parkinson’s disease. However, the classical reaching for food pellets in rodents also has some technical shortcomings and its use under head-fixed conditions is rather limited. The number of trials is typically below hundred, reducing the statistical power. Moreover, mastication of solid rewards introduces unavoidable movement artefacts interfering with electrophysiological and optical recordings.
Here, we explore a novel version of this paradigm in which mice are trained to reach for water droplets instead of food pellets. We found that freely moving mice immediately engage in this water droplet reaching task and become fully proficient after 5 training sessions. After training, mice performed on average 390±34 reaching trials per hour. Importantly, the “reach-to-grasp” kinematics for water droplets follow the same sequence described for classical pellet reaching.

Inspired by the classical “center-out” reaching task in primate, we next investigated whether mice were able to perform the task under head-restrained conditions and towards different target locations. We found that head-restrained mice can rapidly learn to locate, reach out and grab water drops presented in different target locations around their snout. Interestingly, not the whiskers, but the olfactory system is principally used for target localization. Optogenetic inactivation of the motor cortex halted the initiation, as well as the execution of ongoing reaching movements. Finally, more complex sensory-motor association tasks, such directional reaches guided by vibrotactile cues can also be rapidly learned, demonstrating the flexibility of the task.

Taken together, we found that reaching for water has the potential to become a universal and flexible behavioral platform for systems neuroscience research in mice.

D33 Visuomotor coupling shapes the functional development of mouse visual cortex

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The emergence of sensory guided behavior depends on sensorimotor coupling during development. How sensorimotor experience shapes neural processing is still unclear. Here we show that the coupling between motor output and visual feedback is necessary for the functional development of visual processing in layer 2/3 of primary visual cortex (V1) of the mouse. Using a virtual reality system, we reared mice either in conditions of normal or random visuomotor coupling. We recorded the activity of genetically identified excitatory and inhibitory layer 2/3 neurons in response to transient visuomotor mismatches in both groups of mice. Mismatch responses in excitatory neurons were strongly experience dependent and driven by a transient release from inhibition mediated by somatostatin-positive interneurons. These data demonstrate that layer 2/3 of V1 computes a difference between an inhibitory visual input and an excitatory locomotion-related input, where the balance between these two inputs is finely tuned by visuomotor experience.

D34 Gamma suppression in the Basal Forebrain during exploratory behaviour.

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Traditionally the basal forebrain (BF) has been thought of as an activating system providing the major source of cholinergic input to the cerebral cortex where it plays a role in attention, arousal and learning. Apart from cholinergic neurons, GABAergic neurons also project to cortical regions where they play an important role in
modulating neural network state, for example by enhancing responsivity, contrast sensitivity in primary visual cortex (V1). Previously we have shown prominent BF gamma (30-80 Hz) oscillatory activity in an animal’s home cage during wakefulness. In order to study the relationship between BF gamma activity and the cortical LFP during exploratory behaviour we implanted Tungsten electrodes in the BF, V1 of rats. Using miniature wireless device (Neurologger) we continuously recorded the LFP’s in the animal’s home cage and during open field arena exploration. Surprisingly we observed a strong suppression of BF gamma activity during arena exploration compared to gamma activity in the home cage, this suppression was also observable in single unit recordings, localized to the basal forebrain, and was unrelated to the animal’s movement. These results are indicative of a novel, non-activating role for the basal forebrain during exploratory behaviours.

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D35 Bottom-up and top-down mechanisms governing auditory sensory gating in a mouse model

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In association with impaired performance in attention related cognitive tasks, EEG studies of schizophrenic patients repeatedly showed alterations in processing of auditory stimulations and in particular in auditory sensory gating and mismatch negativity. Sensory gating refers to the fundamental property of the brain that down-regulates neural response to a stimulus that is repeated after a short interval. Sensory gating is thought to reflect an inhibitory processing component of attention; however despite the long history of characterization of this phenomenon, the neural mechanisms are not clearly understood. One hypothesis is that sensory gating is governed by top-down influences from the prefrontal cingulate areas on the bottom-up sensory processes. In the present study we address sensory gating neural mechanisms in head-fixed awake mice using either surface EEG or multi-site intracerebral recordings. We use paired tone paradigm with a wide frequency range (white noise) and a variable inter-stimulus interval (ISI). Analysis of global field power from surface EEG recordings revealed sensory gating up to 2s ISI. We describe the activation of a large-scale auditory network propagating from the brainstem to the frontal cortices and we demonstrate a robust attenuation of the response to the second tone that begins as soon as during the feedforward activation of the thalamus by the inferior colliculus. Additionally, time-frequency analysis revealed a theta-gamma coupling between the anterior cingulate cortex and the primary auditory cortex suggesting a top-down mechanism. A delayed increase in beta power in thalamus and delayed firing of a subset of single neurons in the auditory cortex following the first tone support the top down regulation. Ongoing experiments and analysis are directed towards determining further relationships between different areas.
DISTINCT NEURONAL CIRCUIT DEVELOPMENTS EXIST FOR PROCESSING SPECIFIC SOUND FEATURES IN THE BRAIN

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The development of language ability and speech perception depends on segregation of sound features like pure tones (PT), azimuth, intensity and frequency modulated sweeps (FMS) from the auditory environment. Such segregation consolidates during developmental plastic phases called critical periods (CP) when exposure to these features can determinately refine/alter neuronal circuits wiring and functionality. Whether different features have same CPs and are processed by the same neuronal circuits is unknown. The present study compares the developmental plasticity and circuits of two sound features: PT and FMS. The CP for PT in mice is known to occur between postnatal days (P)12 to P15 in the primary auditory cortex (A1). Albeit PT is well characterized, FMS are more prevalent in rodent auditory environment than PTs yet scarcely studied. Using multi-unit electrophysiological recordings in anesthetized mouse A1, we aim to describe the development of responses to FMS and to delineate its CP. Responses (spike rate) to FMS of different rates and direction show dramatic increase between P20 and P30. Exposing mice to a specific FMS for short periods within this window but not earlier has long-lasting effects, like altered sweep direction preference. Since maturation of inhibitory neurons has been linked to shaping CP in other sensory cortices, the amount of different type of inhibitory neurons in A1 during development were quantified with immunohistochemistry. The number of parvalbumin-positive GABA cells in A1 increased significant between P20 and P25. Currently we are testing the involvement of other GABA subtypes. This data shows the presence of a plastic window for FMS between P20 and P30 and a possible effect of parvalbumin-positive GABA neurons density on this developmental plasticity. We next addressed the question that whether the neuronal circuits underlying PT and FMS processing (perception) are discrete. Sound manipulation within the FMS-developmental plastic window did not affect the PT response properties. Conversely, exposing mice to PT during CP for PT altered properties of PT but not those of FMS such as rate and direction selectivity preferences in A1. Additional experiments are performed to determine the independence of both circuits. Together, these results indicate that the PT and FMS are processed by circuits developing asynchronously. The study would help identify neuronal circuits and cells that are plastic during CP, which might ultimately raise new therapeutic possibilities for patients with various sensory deficits.

Experience-dependent spatial expectations in mouse visual cortex

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In generative models of brain function, internal representations are used to generate predictions of sensory input. Visual cues exert a strong influence on the structure of such representations, yet little is known about how internal models influence sensory processing. Here we show that, with increasing experience in a virtual environment, the activity of neurons in layer 2/3 of primary visual cortex (V1) became increasingly informative of spatial location. Strikingly, a subset of V1 neurons exhibited responses that were predictive of the upcoming
visual stimulus in a spatially dependent manner, and a separate subset of V1 neurons selectively responded to the omission of an expected stimulus. We found that stimulus predictive responses emerged in V1-projecting anterior cingulate cortex (ACC) axons, suggesting that ACC serves as a source of predictions of visual input to V1. These results are consistent with a predictive coding interpretation of V1 function, where an internal representation of the visual scene are compared with feed-forward visual input. We are now applying the framework of predictive coding to the development of artificial neural networks. We are aiming to create generative models that can learn internal models of their environment and use them to make context-sensitive predictions of the future, and evaluating these abilities in video games.

D38 Characterizing sleep spindles in mice using optimum wavelet functions

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Spindles are transient oscillatory events (9-16 Hz) occurring in the thalamo-cortical network during non-rapid eye movement (NREM) sleep. To improve the performance of automated identification of spindles, we optimized wavelet function, based on wavelet analysis using local field potentials (LFP), electroencephalogram (EEG) and single/multi-unit recording in mice. Thalamic, cortical, and hippocampal LFP/unit signals were recorded from freely-behaving mice. Signals were analysed by continuous wavelet transform using 15 different wavelet families. Wavelet energy in the spindle frequency band was calculated, and ranked based on ratio between average wavelet energy of spindle segments and spindle-free segments. The frequency B-spline wavelet best captured spindle patterns, increasing energy approximately 25% in comparison to complex Morlet wavelet. We further developed an automated spindle-detection algorithm based on criteria including wavelet energy, thresholding, minimum length and number of cycles, and peak frequency.

On average, 2.83, 2.52, and 2.17 spindles per minute were detected during NREM for thalamic, cortical, and hippocampal regions, respectively. Average spindle duration was 660 ms for thalamus, 580 ms for parietal and occipital cortex, 710 ms for cingulate cortex, and 560 ms for hippocampus. Thalamic recordings were obtained from central medial (CMT), ventrobasal (VB), anterodorsal (AD), and reticular (RTN) thalamic nucleus. Spindling in all thalamic nucleus and parietal cortex showed a highly significant increase within 15 s before transition to REM, while no significant increase was observed for hippocampal (subiculum, CA1, CA3) and other studied cortical (cingulate and occipital cortex) regions. Spindles also indicated a high correlation with slow waves, and a cortical down state preceded spindles.

Furthermore, analysis of single units revealed a highly significant increase in spiking activity of cells (~2-3 times more in comparison to NREM baseline) during spindles within CMT, VB, and RTN, but not within AD. Interestingly, cingulate cortex also showed a notable increase during spindles (~2 times more), while parietal and occipital cortex showed no remarkable increase.
**D39** Interneuron subtype-specific activation of alpha5-GABA receptors controls NMDA receptor activation

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Selective modulation of 5-subunit containing GABAA receptors by negative allosteric modulators (5-NAM) has been shown to improve hippocampus-dependent learning. In the current study, we investigated the underlying cellular mechanisms using whole-cell patch-clamp recordings in the CA1 region of hippocampal brain slices. Application of the 5-NAM RO4938581 reduced slow dendritic inhibitory postsynaptic current (IPSC) amplitude to 64.4 ±14.4% of the control, whereas somatic IPSCs remained unaffected. The dendritic nature of the 5-NAM-sensitive inputs was confirmed by spatially localized GABA release in the presence of tetrodotoxin from interneurons expressing channelrhodopsin (ChR2) under the control of the vesicular GABA transporter promoter. In slices from mice expressing ChR2 in specific interneuron subpopulations, IPSCs evoked in nNOS-Cre and somatostatin-Cre mice were reduced by the 5-NAM whereas those evoked in parvalbumin-Cre remained largely unaffected. Remarkably, application of the 5-NAM increased burst EPSPs up to 137.0 ±15.8% and rectified deficient NMDA receptor activation in Ts65Dn mice, a mouse model of Down Syndrome. Furthermore, impaired theta-burst stimulation-induced LTP in Ts65Dn mice (110.1 ±3.1%; wt: 127.1 ±7.2%) was rescued by acute application of the 5-NAM (122.9 ±6.2%). These results demonstrate that 5-NAM reduces specifically dendritic synaptic inhibition to allow for enhanced NMDA receptor activation essential for learning and memory.

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**D40** Characterizing local connectivity and plasticity in the lateral amygdala, a center for fear learning

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Introduction: Fear conditioning combines an unconditioned stimulus with a conditioned stimulus (CS) so that the CS alone can subsequently elicit fear-related responses. While the convergence of signals onto single lateral amygdala (LA) neurons has been extensively studied, little is known about the role of local recurrent networks in threat memory encoding.

Aims: We hypothesized that threat-related signals are re-integrated in the LA through local neuronal assemblies. To address this, we aimed to characterize the LA’s network organization, including connectivity among memory-participating neurons.
Methods: We used whole-cell patch-clamp recordings to simultaneously access up to 12 neurons at a time. The connectivity of over 563 neurons was assessed by delivering, successively, trains of 8 pulses at 20 Hz and monitoring for evoked excitatory post-synaptic potentials (eEPSP). Neuronal memory-recruitment was assessed by expressing a destabilized GFP under an enhanced Arc promoter, after memory recall.

Results: We observed ~2% connectivity biased towards close-proximity neurons. Analysis of the peak excitatory post-synaptic current amplitudes suggested 1-5 release sites, with a quantal size of 10±3 pA and probability of release of ~0.5 ± 0.2 (±SD). To better understand how this network could encode fearful memories, we performed a spike-timing-dependent plasticity protocol which resulted in a 30% increase in amplitude for the first eEPSP of the stimulus train, while average eEPSP amplitude was unchanged, suggesting a redistribution of synaptic efficacy. Finally, following a memory recall protocol, recruited (GFP+) neurons had greater connectivity (4%), higher eEPSP amplitude (1.4±0.1 mV) and higher probability to observe an eEPSP (0.5±0.04 %) compared to controls (2%, 0.9±0.1mV and 0.4±0.01%, respectively; ±s.e.m.).

Conclusions: The LA network follows a "small-world" network organization, with memory-recruited neurons forming stronger and more numerous connections. This suggest either that enhanced local network excitability favors memory recruitment or that memory recruitment increases connectivity, to be determined by future experiments.

**D41 Optogenetic Modulation Of Sleep Slow Wave After Focal Ischemic Stroke**

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Objectives: Disturbances of sleep-wake cycle and brain state oscillations are frequent after stroke and are associated to negative outcomes. Experimental studies demonstrated that sleep supports the reorganization of neuronal connections and neuroplasticity during stroke recovery. We hypothesize that stroke causes an increase in sleep-like ‘up’ and ‘down’ states in electroencephalogram and local field potential recordings and that this so-called bistability is critical for stroke recovery. To investigate the role of sleep oscillations on brain plasticity following stroke we directly target the neuronal populations in layer V of forelimb somatosensory cortex by combining cell-type specific optogenetic techniques with in vivo electrophysiology.

Methods: We expressed ChR2 (activation), ArchT (inhibition) or mCherry (control) in inhibitory (VGAT) or excitatory (CamKII) deep layer cortical cells of the peri-infarct area to render them light sensitive. Animals were chronically implanted with optical fibers and multiple tetrodes inipsi and controlateral cortical layer V. Experimental stroke was induced by Middle Cerebral Artery Occlusion (MCAO).

Results: Indeed stroke caused sleep disturbances. 24h after stroke down state rate was reduced during slow-wave-sleep in the peri-infarct area, while rapid-eye-movement sleep duration was increased. To optogenetically investigate the contribution of excitatory versus inhibitory cortical neurons to altered sleep oscillations we confirmed the presence of transfected cells within the layer V, forelimb somatosensory cortex through immunohistochemistry. Amongst all the stimulation protocols tested, optical silencing of pyramidal cells in layer V of the cortex robustly induced both LFP and single unit spike activity similar to a down-state of the neuronal
Conclusions: We successfully targeted layer V neuronal cells of the somatosensory cortex in both transgenic and wild type mice and showed that optogenetical induction of down-state is possible and represents the first step in the modulation of sleep-like oscillations. Comparing stimulation before and after stroke will reveal possible altered susceptibility to down state-induction.

**D42 Membrane potential dynamics of specific neurons in layers 2/3 and 4 of mouse barrel cortex**

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The network operations in the neocortex are mediated by the interactions between diverse neuron types. However, the functional roles of specific neuron types in awake behaving animals are poorly understood. Here, we performed whole-cell recordings in the primary somatosensory barrel cortex of awake, head-restrained mice under two-photon imaging. The membrane potential dynamics of excitatory, parvalbumin-expressing (PV), somatostatin-expressing (Sst), and vasopressin-expressing (VIP) neurons in layer 2/3 (L2/3) and layer 4 (L4) were recorded during spontaneous whisking in air, and active sensation. During spontaneous whisking, the membrane potentials of L2/3 and L4 excitatory neurons changed only modestly. The membrane potentials of L2/3 and L4 PV neurons depolarized. L2/3 Sst neurons hyperpolarized during whisking, whereas L4 Sst neurons depolarized. L2/3 VIP neurons were depolarized and increased firing during whisking. In response to active touch sensation, L4 excitatory neurons received fast EPSPs. In L2/3 and L4 Sst neurons, transient inhibition was often observed on touches, but this was followed by prolonged excitation. In L2/3 VIP neurons, membrane depolarization often preceded touches. All data as well as analysis code are publicly available.

**D43 Suckling behavior and the resulting milk ejection recruit a local network in the PVN that includes oxytocinergic neurons**

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Introduction: In addition to shaping social interactions, oxytocin (OT) is involved in milk delivery via lactation. In particular, oxytocinergic neurons develop bursting activity during suckling behavior. In rodent models, OT injections can optimize baseline neuronal firing and increase burst amplitude and frequency, effects that see a decrease with OT antagonist. However, neither the effects of endogenous nor exogenous OT have been studied at the network level.

We hypothesize that network activity of oxytocinergic neurons during mother-pup interaction can be modulated by the oxytocinergic system, either via external applications or endogenous release.

**Aims:** Probe oxytocinergic neuron network activity in the local field potential (LFP) following endogenous OT release. Furthermore, we aim to link network activity to oxytocin sensitivity and optogenetically confirm location of tetrode.
Methods: We performed long-term in vivo electrophysiological recordings in the awake female rat, in the presence of her pups (P3 to P21). To this end, we employed an optrode (32-channel tetrodes with optical fiber) targeting the oxytocinergic magnocellular neurons of the paraventricular nucleus of the hypothalamus (PVN). This latter population of neurons expressed Channelrhodopsin2 (ChR2) under the oxytocin promoter.

Results: During suckling, LFP synchronicity was evident at theta (5-10 Hz) frequencies, while ripples (140-200 Hz) were also observed. Importantly, the high-bursting neurons previously characterized in the literature and associated with suckling were active during theta-band activity. Interestingly, it was possible to replicate synchronized theta activity by intranasal OT administration in the virgin rat.

In order to confirm the location of our tetrodes, blue light stimulation in the PVN triggered synchronized activity among oxytocinergic neurons, confirming the correct location of the tetrodes. Furthermore, blue-light activation during pup-suckling led to a decrease in the amplitude of spontaneous bursting, as well as a disruption of the periodicity, highlighting the importance of an optimal stimulation frequency to mimic endogenous conditions.

D44 Functional Organization of the Visual Cortex of the Mouse Lemur

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Neuroscience research using rodents as an animal model relies on the assumption that results should generalize across species to primates and ultimately to humans. However, many brain areas, including the neocortex, have species-specific functional organizations. To identify common traits or differences in the circuit organizations of primates and rodents, one must find a way to match brain size, recording methods, and behavioral paradigms. The mouse lemur (Microcebus murinus), the world smallest primate, enables this comparison. It is comparable to the mouse in most aspects, but its functional brain anatomy is literally uncharted.

We have recently started exploring the functional organization of the mouse lemur cortex by adapting a series of optical imaging, molecular and behavioral tools which were initially developed for rodents. Our preliminary results show that these cutting edge tools can rapidly be transferred to this primate. We have successfully performed intrinsic optical signal imaging through chronic cranial windows and revealed clear orientation selective maps in the primary visual cortex. Such maps are a classical hallmark of the primate cortex and seem absent in rodents. Currently we are analyzing our preliminary data to search ocular dominance columns, which have been found to be highly variable in other primates, such as in squirrel monkeys. We will also present the first high-throughput behavioral paradigms for mouse lemurs which were developed to probe their visual psychophysics.

Taken together, these early findings suggest that the mouse lemur has great potential to become a valuable alternative primate model in systems neuroscience and will thus complement current trends of large scale, mouse-centric efforts to understand brain circuits.
Deciphering the role of mGluR4 and mGluR7 in modulating the reward pathway between amygdala and nucleus accumbens

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The amygdala plays a key role in emotional learning, specifically on the acquisition and processing of fearful and rewarding associative memories. Processing begins with an external sensory stimulus (mostly via thalamus) relaying onto basolateral complex of the amygdala (BLA), and then onto the nucleus accumbens (NAc). BLA-NAc projections are believed to mediate reward-seeking behavior, and are implicated in substance abuse. Group III metabotropic glutamate receptor (mGluR) signaling (specially mGLUR4 & 7) is involved in emotional learning and is largely found presynaptically on the thalamus-to-amygdala synapse. However, the expression and function of mGluRs on the BLA-NAc synapses has not been thoroughly studied. Interestingly, altering glutamate signaling in the BLA-NAc circuitry has been linked to self-stimulation and drug-seeking behaviour. A deeper understanding of BLA and NAc interplay is essential for therapeutic agent development targeting substance abuse, and other neurological and neuropsychiatric illnesses.

In order to characterise these connections, we first identified BLA neurons that specifically project to NAc by retrograde tracing (retrobeads) and then assessed the role of allosteric modulators (developed by our collaborators, Addex Therapeutics) of mGluR4 (PAM4) and mGluR7 (NAM7) on in vitro basal synaptic transmission. Fluorescent bead injection in NAc labeled a high percentage of BLA neurons (> 50%). Furthermore, when PAM4 was applied, 78.6% of cells demonstrated a decrease in the frequency of sEPSCs, compared to control (PAM 4: 52.4% ± 7.4 [n=11] vs ACSF: 102.7% ± 9.5 [n=8]). In contrast, when NAM7 was applied, the majority (72.7%) of cells responded with increase in sEPSCs frequency compared to control (NAM7: 163.4% ± 18.3 [n=11] vs ACSF: 9.0% ± 12.9 [n=8]). The effects of both allosteric modulators on the frequency of sEPSCs were reproducible (PAM4: 50%, and NAM7: 80%). Taken together, we conclude that mGluR4 and mGluR7 are functionally expressed in BLA and can modulate the activity of BLA pyramidal neurons that project to NAc. This work expands our toolset for future experiments focused on assessing the role of mGluRs in reward and goal-oriented behavior, and the development of therapeutics agents for neuropsychiatric disorders.

Effect of redox dysregulation on adult hippocampal neurogenesis in a mouse model of schizophrenia

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Schizophrenia (SZ) is a major psychiatric disease with high heterogeneity of symptoms, one of them being cognitive deficit, which cannot be improved by available treatments. It has been suggested that impaired adult hippocampal neurogenesis (AHN) may contribute to the cognitive deficit observed in patients. Indeed,
hippocampal volume reduction is a robust observation in postmortem brains of patients and some studies also found a reduction of neural progenitors. Moreover, several animal models for SZ, such as DISC1 deletion and maternal immune activation, also show decreased AHN. Several factors are known to modulate AHN, including the redox state, inflammation, as well as parvalbumin expressing fast-spiking interneurons (PVI), which are key players in SZ pathophysiology.

The aim of this study is to investigate whether the interaction between these 3 main factors may lead to impaired AHN. We took advantage of a mouse model for redox dysregulation, the GCLM KO mice, that show SZ related phenotype. These mice have 70% decreased glutathione, an important antioxidant, and increased oxidative stress in the brain throughout life, as well as decreased PVI in the ventral, but not dorsal, hippocampus, which was related with impaired behavior related to this specific region (Steullet et al., 2010). We investigated the proliferation rate of hippocampal progenitors and newborn neurons survival in the dorsal versus ventral hippocampus of adult GCLM KO and WT mice, using BrdU incorporation assays. Preliminary data show a dysregulation in the proliferation and survival of newborn neurons in the GCLM KO dentate gyrus. These results suggest that the oxidative stress level in the dentate gyrus of the GCLM KO mice may affect AHN. Further investigation will bring light on the mechanism underlying the involvement of redox and immune dysregulation, as well as PVI, on neurogenesis impairments in SZ.

E. Cognitive and Behavioral Neuroscience

E1 Visual Reinforcement of Illusory Rotations during Centrifugation: A Novel Habituation Strategy to Motion Sickness

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Background: Artificial gravity (AG) is the only countermeasure providing an “Earth-like” solution to weightless health hazards. Head movements during centrifugation, however, cause motion sickness (Cross-coupling stimulus) due to conflicts between perceived, though illusory, rotations and sensed gravity direction. Existing habituation protocols successfully abate motion sickness. The reduction of the conflict supposedly occurs by decreasing vestibular responses to rotation (as quantified by reflexes), i.e. adapting the semicircular canals contribution to the multi-sensory integration generating self-motion perception. In outer space, however, perception of self-rotation has an important role in self-motion sensing, as astronauts are already deprived of gravity reference. The aim of this research is to evaluate if a different adaptation is possible, abating motion sickness without decreasing response to rotation.

Methods: We tested 19 healthy subjects on the ESA Short Arm Human Centrifuge at DRL, Cologne. The control group (CG: 9 subjects, 3 f) performed a “standard” habituation protocol consisting of 30° clockwise head rolls during centrifugation at 100°/s (1 g at feet). The test group (TG: 10 subjects, 5 f) performed an identical protocol, with the addition of visual stimuli triggered by head movements providing optokinetic stimuli matching the predicted vestibular sensation. Motion sickness was measured using a 1-20 scale, while an eye tracker recorded the vestibulo-ocular reflex (VOR). Measurements were repeated after 24h.
Results: Only 15 subjects (7 CG, 8 TG) completed the experiment. The same reduction of motion sickness from day 1 to day 2 was observed in both groups (median [MAD] CG: -4 [2]; TG: -4 [1], p=0.78). The CG had a significantly larger reduction of the VOR duration than the TG (CG: -4 [1] s; TG: -1 [2] s, p=0.05).

Conclusions: Subjects habituate even if illusory self-rotation induced by head tilts is sustained by visual input. Visually reinforced habituation preserves vestibular reflexive responses to rotations and it is therefore a good candidate to achieve an alternative adaptation of multi-sensory integration that preserve rotation sensing but abate motion sickness in AG.

E2 In the pursuit of the fear engram: Identification of neuronal circuits underlying the treatment of anxiety disorder

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Fear and other anxiety disorders are extraordinarily robust and difficult to treat. Among the most effective treatments for anxiety disorders are exposure-based therapies, during which a patient is repeatedly confronted with the originally fear-eliciting stimulus in a safe environment so that the once fearful stimulus can be newly interpreted as neutral or safe. A fundamental element for successful exposure-based therapies is the reactivation/recall of the traumatic memory, which initiates a time-limited process called memory reconsolidation, during which a memory becomes susceptible to disruption.

Presently, the neuronal subpopulations underlying successful fear memory extinction remain completely unknown, which represents a big gap in memory research. Therefore, we aim to identify these neuronal subpopulations that are causally implicated in effective attenuation of remote fear memories in order to determine whether the original traumatic memory trace has been permanently modified or a new memory trace of safety has been superimposed over the original one. Using exposure-based therapy in transgenic mice, which allows for a time-limited activation of neurons upon remote memory recall, making it not only possible to visualize those neurons but also to experimentally isolate them from the rest of the neurons for further molecular investigations.

E3 Stimuli associated with food rewards influence goal-directed behavior in overweight, obese and normal-weight individuals

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In our everyday lives, we are surrounded by cues (e.g. advertisements) reminding us of palatable food. It is believed that this “obsogenic” environment may lead to excessive food consumption and is therefore, contributing to the increasing prevalence of overweight and obesity. Previous research has shown that not all individuals are equally susceptible to these reward-predicting cues as potentially reflected by two different learning styles (i.e. goal- versus sign-tracking).

The aim of the present pilot study was to investigate the individual learning style my means of eye tracking
using a Pavlovian-to-instrumental transfer (PIT) task in an overweight (ow), obese (ob) and normal-weight population (N normal-weight = 10, Now/ob = 17).

Preliminary results showed that the food-related stimuli influenced goal-directed behavior significantly (PIT effect, p < 0.05). The BMI correlated negatively with this PIT effect (r = -0.34, p < 0.05) and learning style correlated with the total impulsivity score (r = 0.349, p < 0.05). More detailed analyses revealed a trend suggesting that the largest PIT effect was found for overweight participants, particularly when they are goal-trackers. The trend in our data is in favor of the hyper- vs. hyposensitivity theory of reward in obesity predicting an inverted U-shaped relationship between BMI and reward sensitivity.

A novel tablet application for evaluation of activities of daily living in patients with Alzheimer’s Disease: preliminary results

E4

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Alzheimer’s disease (AD) is the most common form of dementia and it’s characterized by a decline in cognition and impaired activities of daily living. Laboratory tests are common methods in order to evaluate the cognitive abilities. However, these tests do not indicate the functioning in daily living. To investigate the performance in instrumental activities of daily living (IADL), questionnaires are used. These questionnaires have the disadvantage of being subjective and being under the influence of patient’s anosognosia. Thus, Serious Games offer the possibility to recreate a virtual environment with daily living activities and cognitive evaluation. It has also the advantage of being motivating and fun for the participants. Additionally, while ecological assessment involves identifying and addressing individual needs and goals, tablet based rehabilitation program allow patients to train independently at home with targeted goals for each patient according to their own difficulties.

The idea of the present study was to develop and evaluate a new Serious Game based assessment tool, developed on a tablet, for patients with Alzheimer’s disease. 7 patients (2 Male, Age M = 80.7; MoCA M =29.3) and 13 healthy controls (11 Male, Age M= 75.7; MoCA M = 19.3) were recruited to participate in this study.

A virtual scenario consisting of 6 daily living tasks was created: three navigation tasks, a shopping task, a cooking task and a table preparation task. The goal of the game was to accomplish these 6 daily living activities following a story line. If they didn’t remember what they had to do during the game, they had the possibility to press the button “Instructions” which was always available on the screen. Outcome measures to evaluate several cognitive functions were recorded, i.e. overall duration time and inactivity time, time and inactivity pro task, ingredients recall, number of time participants requested reminders for instructions. Additionally, participants rated their degree of satisfaction about the game with the System Usability Scale, a questionnaire developed to evaluate the effectiveness, the efficiency and the participants’ satisfaction about the application. Preliminary results indicate a significant difference in the overall time for achievements of the tasks and in the overall inactivity time. Furthermore, a significative difference in duration and inactivity time for navigation,
cooking and shopping were found. No difference was found for the table preparation task. Additionally, patients with AD recalled significantly less ingredients then healthy participants and needed significantly more requests for instructions reminders.

Results about the usability of the game suggested that both patients and healthy participants found the game user-friendly. This study suggests that the new Serious Game tablet based assessment tool is an ecological way to evaluate cognitive abilities and it allows to distinguish Alzheimer's patient’s performance from healthy controls and offer a good basis for intervention targeted program.

E5 Acute physical exercise improves memory consolidation in humans via BDNF and endocannabinoid signaling

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Regular physical exercise enhances memory functions and neurogenesis in the hippocampus. In animals, a single session of physical exercise has been shown to increase the levels of BDNF (Brain Derived Neurotrophic Factor), which is linked to increased neurogenesis and plasticity in the hippocampus. Further, it has also been shown that acute exercise increases the release of endocannabinoids (especially anandamide (AEA)), small lipophilic molecules affecting dopaminergic transmission and which further enhance the release of BDNF. Whether these effects are preserved in humans is unknown. Here, we combined blood biomarkers and cognitive tasks to assess the effects of medium and high intensity acute physical exercise on memory functions and underlying biomechanisms in humans. Our hypothesis is that medium intensity exercise improves memory through enhanced BDNF / endocannabinoid signaling, while high exercise intensity causes physical stress detrimental to cognitive functioning. We tested twenty healthy young participants at three time points using an associative memory task: each visit consisted of a learning and a test part separated by an exercise (moderate or high intensity) or a rest session, two blood samples were taken at each visit before and after the exercise or rest segments. Our results show a significant increase in performance in the memory task after exercise at a moderate intensity but not high intensity, compared to after rest. Participants responded also significantly faster and were more certain of their correct responses selectively after moderate intensity. Concerning biomarkers, we report significantly higher levels of BDNF and of the endocannabinoid AEA after exercise compared to rest. Further, increase in AEA and hippocampal activation was linked. Overall, our results shed light on the biomechanisms elicited by acute physical exercise to improve cognitive functions.

E6 Coordinated infra-slow neural and cardiac oscillations mark fragility and offline periods in mammalian sleep

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Rodents sleep in bouts lasting minutes, humans sleep for hours. What are the universal needs served by sleep given such variability? In sleeping mice and humans, through monitoring neural and cardiac activity, combined
with assessment of arousability and overnight memory consolidation, respectively, we find a previously unrecognized hallmark of sleep that balances two fundamental, yet opposing needs: to maintain sensory reactivity to the environment while promoting recovery and memory consolidation. Coordinated 0.02 Hz-oscillations of the sleep spindle band, of hippocampal ripple activity and of heart rate divide non-rapid eye movement sleep (non-REM sleep) sequentially into offline phases and phases of high susceptibility to external stimulation. A noise stimulus chosen such that sleeping mice woke up or slept through at comparable rates revealed that offline periods correspond to raising, whereas fragility periods to declining portions of the 0.02 Hz oscillation in spindle activity. Oscillations were present throughout non-REM sleep in mouse, yet confined to light non REM sleep (S2) stages in human. In both species, the 0.02 Hz oscillation predominated over posterior cortex. The strength of the 0.02 Hz-oscillation predicted superior memory recall after sleep in a declarative memory task in humans. These oscillations point to a conserved function of mammalian non-REM sleep that cycles between environmental alertness and internal memory processing in 20-25 s intervals. Perturbed 0.02 Hz-oscillations may cause memory impairment and ill-timed arousals in sleep disorders.

E7 Neurodegenerative Loss of Amygdala Inhibition and Hyper Anxiety

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This research project aims to examine hyper-anxiety in patients with beginning cognitive disorders. Emotional symptoms, including anxiety, are frequently observed in beginning cognitive disorder patients and present a major difficulty for both patients and caregivers, but they remain poorly understood.

This project focuses on the role of the amygdala in these symptoms, as the amygdala is known to be a critical brain region for anxiety behaviours, and amygdala atrophy is a common early neurological sign of beginning cognitive disorder and Alzheimer’s disease (AD) patients. Two sub-nuclei of the amygdala are of particular interest – the Basolateral Amygdala (BLA) and the Central Amygdala (CeA). The CeA is important for the unconditioned, instinctive fear response, whereas the BLA is more cortical and is thought to exert modulatory control over CeA function. Recent evidence suggest that the amygdala damage in early cognitive disorder and AD patients is limited to the BLA, while the CeA remains intact.

We aim to gain greater insight into the role of the amygdala in anxiety in these patients by comparing them to a South African population of patients with a very rare genetic condition known as Urbach Wiethe Disease (UWD). Recently it has been shown that in these patients, UWD has led to bilateral loss of the basolateral amygdala (BLA). Moreover, detailed fMRI has shown preserved function in the CeA. Hyper-anxiety has been demonstrated in these subjects, likely arising from a loss of inhibitory control of the BLA, and consequently the prefrontal cortex, over the CeA. Hyper-anxiety in beginning cognitive disorder patients may similarly stem from a loss of inhibitory control of the BLA, and the prefrontal cortex, over the CeA.

In an attempt to investigate amygdala functionality we run a threat and escape task (TAET) which manipulates the proximity of a threat in order to differentially activate OFC-BLA pathways (by distal threat) and the CeA-brainstem pathway (by proximal threat). Previous research has shown that it is possible for OFC-BLA networks to inhibit the CeA-brainstem driven eye blink startle-reflex during effortful flight-responses, but that this ability is lost when a threat becomes so proximal that it is unavoidable, and we replicate this finding here. However,
this OFC-BLA inhibition of the startle reflex in response to escapable threat has been shown by our colleagues in South Africa to be impaired in UWD patients, and we predict that early cognitive disorder patients will show similar impairment.

### E8

**Prior knowledge is sufficient to trigger “mirror activity” when observing grasping movements of another person**

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Observers are able to infer the action intentions of other people in a seemingly effortless way. Studies using transcranial magnetic stimulation (TMS), a non-invasive technique which can assess corticomotor excitability, consistently demonstrated that the observer’s primary motor cortex (M1) becomes facilitated in a muscle-specific manner and that excitability changes are time-locked to the observed kinematics as movements unfold. However, when informative cues are available before an actor initiates the movement, anticipatory motor activity can be decoded from the observer’s M1 even before the actual grasping kinematics are visible. Here, we explored whether these muscle-specific modulations in corticospinal activity occur in conditions in which actions are preceded by informative cues but the movement kinematics are not shown at all. We measured motor-evoked potentials (MEPs) induced by single-pulse TMS to M1 while participants observed either whole-hand (WHG) or precision grasping (PG) action videos which were either fully visible or where grasp-specific kinematics were covered. Furthermore, each movement was preceded by a contextual cue which was associated with a specific grasp and which could be used for predicting the upcoming action. Previous work investigating both action preparation and observation has indicated that the index finger (FDI) is stronger activated during PG than WHG while the little finger (ADM) is stronger activated during WHG than PG. Here we used grip specific modulation of FDI and ADM excitability as the main outcome parameter. To do so, we divided the mean amplitude of MEPs collected while observing a WHG by the MEP mean amplitude while observing a PG (ratio = MEPWHG/MEPPG), separately for each muscle and condition. Grip specific modulation is inferred when MEPWHG/MEPPG ratio is bigger than 1 for the ADM and smaller than 1 for the FDI. First analyses revealed that the MEPWHG/MEPPG ratios exhibited significant grip-specific modulation when the observed movement kinematics were fully visible confirming previous results. Importantly, grasp-specific modulation still reached significance when the grasping kinematics of the observed movements were covered but the grip type could be predicted based on the informative cue. This suggests that when participants receive prior information on the upcoming grip type, corticomotor excitability measured in the observer’s M1 exhibits grip specific modulation irrespective of whether the grip kinematics are present or not.

### E9

**The contribution of circulating factors to non-genomic inheritance in mice**

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Adverse environmental conditions experienced early in life constitute a major risk factor for the development of
neuropsychiatric pathologies in adulthood. Such pathologies, often resulting in emotional and cognitive impairments, are largely implicated with epigenetic components. Our lab uses a robust paradigm of unpredictable maternal separation combined with unpredictable maternal stress (MSUS) to model emotional and cognitive impairments associated with chronic exposure to early traumatic experiences. This model has established that, in addition to a behavioral phenotype, epigenetic aberrations developed in the exposed mice can be passed to offspring with no exposure to adverse environmental conditions. Although the epigenetic involvement in these studies is unmistakable, the mechanism responsible for inducing transmissible epigenetic changes requires additional characterization. Owing to the physiological response to traumatic experiences, the release of signaling factors into the bloodstream could initiate a cascade of events resulting in differential regulation of the epigenome in progenitor germ cells. When the progenitors become mature sperm cells, they will carry the alterations to the next generation. Here we use a combination of unbiased, high-throughput proteomic and metabolomic approaches to assess the functional contribution of differentially regulated circulating factors to the MSUS phenotype. This multi-system analysis shows initial promise in delineating the molecular consequence of early life exposure to adverse environments and ultimately augments our understanding of epigenetic inheritance.

E10 Relationships between Heschl’s Gyrus gyrification, dyslexia and reading performance

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Differences in auditory cortex anatomy have been found in dyslexia, but few have examined these in relation to compensation and/or measures of performance. Very variable gyrification patterns have been observed normatively in Heschl’s gyrus (HG): single HG, common-stem supplication and complete posterior duplication. Higher rates of HG duplication have been found in this disorder, whereas paradoxically in controls, left HG duplication has been associated with ease in foreign sound learning and with phonetics expertise. In the present study we investigated 1) differences in HG gyrification between uncompensated dyslexic, compensated dyslexic and control adults, 2) associations between HG gyrification, dyslexia and reading performance.

94 age-matched participants (21.2±0.5 years old), including 35 controls, underwent a T1-weighted Magnetic Resonance Imaging. Performance on reading and spelling tests served to determine compensation status. 32 individuals were identified as non-compensated dyslexics based on poorer spelling/reading scores than the other and 27 individuals were compensated – their scores did not differ from the controls. HG gyrification patterns were visually identified using the T1. We show a higher rate of left complete posterior duplication in dyslexics irrespective of compensation status compared to controls, in line with the idea that a large second HG could be among the anatomical risk factors for this disorder. Secondly using an ANCOVA on reading performances (NART test) in a subsample of 69 participants, whom behaviour and demographics were fully documented, we report a main effect of dyslexia status (compensated, uncompensated dyslexics, controls), as well as an interaction between dyslexia status and left HG gyrification type. Indeed, the reading performance differed with left HG type together with dyslexia status. The relationship between functional recruitment of HG subregions and their implication in compensation remains to be determined.
Human visual cortex responses to naturalistic auditory and visual speech

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Speech is multisensory by nature: we must move to speak, and these movements, which are visible to our interlocutors, complement the auditory information transmitted by the voice. Cerebral cortex is also essentially multisensory: even primary sensory cortices are sensitive to stimuli from modalities other than their own. Here, we explored how human visual cortex processes naturalistic audiovisual speech using intracranial EEG (iEEG) in patients with drug-resistant epilepsy.

We recorded cortical responses to 10-s long stories consisting of naturalistic speech (modalities: AV, audiovisual; V, visual only; A, auditory only). iEEG electrodes were localized by co-registering pre-and post-implantation MRI and CT scans. We quantified cortical responses to speech stimuli by computing power in the alpha (8-13 Hz) and high-gamma frequency ranges (HGP, an index of local neuronal firing; 70-170 Hz). We defined visual cortex as those electrodes that lay in the occipital lobe and showed increased HGP to V speech stimuli, compared to the pre-stimulus baseline.

Visual cortex responded to V and AV speech with a robust and sustained increase in neuronal activity, which dipped lower for AV than for V speech between 600 and 1200 ms into the stimulus before reaching a stable plateau. In contrast, HGP increased in delayed and crescendo fashion to A speech, rising above baseline about 1 second into the stimulus. Alpha power dropped in marked and sustained fashion in response to V and AV speech (more so for V than AV speech), whereas it slowly decreased in response to A speech. There was a significant negative correlation between HGP and alpha power in response to A speech, but not to V and AV speech.

Our findings extend those of Schepers and colleagues (Cereb Cortex 2015), who recorded iEEG responses to single-word stimuli. The delayed HGP increase in visual cortex in response to purely auditory speech, and its negative correlation with the reduction in alpha power, suggest that crossmodal sensory inputs modulate neuronal firing in visual cortex through oscillatory mechanisms.

Encoding of vigilance state and feeding behaviors by GABAergic neurons in the lateral hypothalamus

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In mammals, the sleep-wake cycle and feeding are conserved behaviors engaging a broad range of brain regions. The hypothalamus has a key role in the integration and regulation of these two behaviors as it receives information from intra- and extra hypothalamic networks. Here, we investigate how GABAergic cells in the lateral hypothalamus (LHGABA) modulate food intake, sleep and arousal.

We selectively manipulated neuronal activity by targeting expression of channel-rhodopsin 2 (ChR2) to LHGABA cells in the lateral hypothalamus from tg(vgat)::cre freely-moving mice. Stimulations at different light intensities lead to rapid arousal from NREM but not REM sleep. When the light pulses were delivered semi-chronically during wakefulness the animals increased their food consumption and the number of feeding events.

To investigate whether the effects on sleep and food intake are mediated by the same cells we monitored neuronal Ca2+ transients from LHGABA expressing GCaMP6s from freely-behaving mice via an integrated miniature fluorescence microscope. We found subsets of LHGABA neurons showing maximal activity in different sleep stages, REM-max and wake-max being the largest sub-populations. These two groups also showed changing activity at the very sleep state transitions. After a 4h sleep deprivation the wake-max neurons significantly decreased their activity during wakefulness but not NREM, whereas no changes were seen for REM-max cells. When investigating food intake behaviors we found neurons to group into food intake-max, food approach-max and feeding unrelated-max subsets. Interestingly, the more specifically a neuron was activated in food intake only the more specifically it was also active in REM sleep.

These findings indicate that LHGABA are multi-functional encoding aspects of both, sleep- and metabolic function. Furthermore they may propose that neuronal reactivation in REM sleep also takes place in circuits for homeostatic integration.

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**E13**

**Thalamic burst firing controls the spatiotemporal diversity of cortical sleep spindles.**

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Non-rapid eye movement (non-REM) sleep is a natural behavioral state during which various rhythmic electrical activities develop in the brain. Amongst these, sleep spindles are key constituents of the cortical spontaneous activity and are supposedly important for brain plasticity and memory consolidation. Spindles are generally described as 0.5-1 s oscillatory events in the 8-15Hz frequency range, known to originate from the reticular thalamic nucleus (nRt) through CaV3.3-type Ca2+ channel-dependent bursts (Astori et al., 2011). However, spindles display considerable spatiotemporal heterogeneity across cortical areas, raising controversies about their sources, cortical topology and function.

To overcome this limit, through in vitro and in vivo recording in wild-type and CaV3.3-/- KO mice, we explore the palette of regional activities within the sleep-spindle generator (the nRt) and we examine the local variations of spindles in multiple cortical areas.

First, we found that nRt neurons in vitro show heterogeneous bursting properties, i.e. somatosensory (S1) versus limbic cortical areas (medial prefrontal cortex, mPFC), arising, at least in part, from unequal recruitment of CaV3.3 channels. We then investigated in vivo local variations of spindle features in head-fixed sleeping mice (wild-type and CaV3.3-/- KO mice) via local field potentials (LFP) from high-impedance (10-12 MOhm) electrodes chronically implanted in the dorsal hippocampus (dCA1) and in somatosensory (S1 and S2), auditory (AC), piriform (Pir), and mPFC cortices. Behavioral states and typical NREMS activities were assessed through conventional
polysomnography (EEG-EcoG/EMG). Our major results in vivo show a functional specification in somatosensory areas mediated by the CaV3.3 channels. Indeed, in CaV3.3-/- KO mice (1) relative spindle power decreased specifically in somatosensory areas (S1 and S2), (2) discrepancies between areas in intra-spindle dominant frequency disappeared and finally (3) spindles tended to be shorter although more recurrent in S1 and S2. By computing cross-correlations in the spindle band, we explored the functional organization of the 6 recorded areas. We identified a clustering of spindles in functional areas (group frontal P1-mPFC, versus group parietal S1-S2-A1) that was lost in the CaV3.3-/-KO and replaced by a global synchronization. Finally, we found that specifically for S1 and S2 the temporal coupling of spindles to the upstate of the cortical slow oscillation (below 1Hz) was perturbed.

Our study shows that molecular and cellular properties of nRt are critical to shape not only the local specificity of cortical spindles but also their coordination with cortical rhythms. These findings will advance the comprehension of how different spindle types emerge in the cortex and could motivate new research on differential capability of learning in different brain areas.

E14 -waves and ripples in human mesial temporal ECoG during viewing of dynamic fearful faces

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Introduction: The processing of fearful faces elicits a hemodynamic response in the mesial temporal lobe but the electrophysiological correlates are yet to be clarified.

Methods: Seven epilepsy patients with electrodes implanted in the mesial temporal lobe were visually stimulated with dynamic sequences of fearful faces (7 times 24s), interleaved with sequences of neutral landscapes. We analyzed the spectral amplitude in the - range (f<10 Hz) and detected high frequency oscillations (HFOs, 80-500 Hz).

Results: The - power in the amygdala and the HFO amplitude in hippocampus were reduced during the face condition as compared to the land condition (paired Wilcoxon test, p<0.05). - power band power and FR amplitude were correlated in amygdala during the land but during the face condition.

Conclusions: Consistent with the hemodynamic response, the amygdala stood out also in electrophysiological recordings. The blocking of - power and of its correlation with FR amplitude in the amygdala during viewing of dynamic fearful faces may reflect cognitive processing, while HFO might regulate the functional connectivity in the mesial temporal lobe.

E15 Reward triggers spontaneous neural reactivation during sleep

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Sleep favors the reactivation and consolidation of newly acquired memories. Yet, how our brain selects the noteworthy information that will be reprocessed during sleep remains largely unknown. From an evolutionary perspective, individuals must remember information that promotes survival or reproduction, such as avoiding dangers, finding food or sexual partners, or (in humans) obtaining money or praise. Here we tested whether events yielding a positive outcome are likely to be reactivated in priority during sleep. Using functional MRI and a brain decoding approach, we show that patterns of brain activity observed during prior waking behavior spontaneously reemerge during slow-wave sleep. Critically, we report a privileged reactivation of neural patterns associated with a rewarded event (i.e., winning at a game). Finally, brain regions reactivated during sleep correlated with better memory. Our study uncovers a neural mechanism whereby the most valuable elements of our lives are getting engraved on our memory while we sleep.

**E16** Rapid learning of auditory discrimination via observation and its limited generalization

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Learning to imitate members of your own species in order to survive is a trait that has been identified in social animals such as humans, non-human primates, and several avian species. Typically, successful imitation is reported when observing animals selectively mimic complex motor behaviors performed by expert demonstrators. For example, songbirds such as the Zebra Finch (Taeniopygia guttata) have the capability of vocal learning by imitating the songs of a tutor experienced early in life. However, little is known about the ability of zebra finches, a highly social species, to learn simple stimulus-response mappings from demonstrating conspecifics. Here, we investigate whether adult zebra finches have the capacity for observational learning of a difficult auditory discrimination task. Briefly, pairs of adult zebra finches were placed in adjacent cages in sound isolation chambers, with one bird acting as a ‘Demonstrator’ for the other, the ‘Observer’. In the first phase of the experiment, the Demonstrator is trained to discriminate between short and long renditions of a typical zebra finch song syllable. 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. A special perch is used by the Demonstrator to trigger stimuli and/or air-puffs, as well as 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 are significantly faster than Demonstrators at achieving the performance criterion. A control group that was exposed to several stimulus and reward cue (sound of air-puff) pairings prior to the actual training period did not show a similar increase in learning rate, allowing us to reject perceptual learning as the mechanism of accelerated learning in observers. We also show that prior knowledge of stimulus value does not provide observers the ability to rapidly learn stimulus-reward associations, allowing us to reject observational conditioning as well. Furthermore, we show that observers are slower than demonstrators at generalizing their learned behavior to new instances of the same stimulus, a novel result in the imitation learning field. Finally, we present preliminary findings which suggest that vocal communication between the birds plays an important role in producing the benefits of observation.
Role of Vasopressin in the regulation of social behavior in the rat Ventral Tegmental Area

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Arginine-Vasopressin (AVP) is a neuropeptide playing an important role in the regulation of social behavior such as social recognition, pair bonding, partner preference and aggression. It is expressed in the paraventricular nucleus (PVN) of the hypothalamus, suprachiasmatic nucleus (SCN) and in extra hypothalamic areas such as Bed Nucleus of Stria Terminalis (BNST) and medial amygdala. The vasopressin receptor (V1aR) can be found in hippocampus, striatum, BNST and ventral tegmental area (VTA), regions important for social behavior regulation.

We used the rat Valproate model of autism to test the role of V1a antagonism on social behavior. Rats were exposed in utero to valproate at day 12.5 of gestation and developed cognitive and social impairments after birth. 7 days of chronic treatment with a Roche V1a antagonist restored normal cognitive and social behavior by normalizing LTP in the hippocampus and restoring normal brain perfusion in piriform cortex, dorsal striatum and VTA as measured by functional magnetic resonance imaging (fMRI) in adult rats. We decided to focus our follow-up studies on the VTA, a heterogeneous structure playing a key role in motivation and reward processing, because it showed the most drastic changes in fMRI and the strongest effect of V1a antagonist drug treatment.

The aim of the present project will be to dissect and characterize the circuitry through which vasopressin regulates the activity of the VTA. To address these questions we have started to use a combination of different in vitro and in vivo approaches. To assess projections from the PVN to the VTA we have injected fluorescent latex beads in the VTA and found retrograde fluorescent label in neurons in the PVN. In parallel labeling with an antibody against vasopressin has revealed AVP positive cells in the PVN and SON. Both techniques will now be combined to assess AVP containing projections from the PVN to the VTA. To investigate the microcircuitry in the VTA that underlies the effects of AVP we have started to perform patch-clamp recordings on dopaminergic and GABA-ergic neurons in combination with AVP and V1a receptor inhibitors. These findings have shown that vasopressin leads to an increased spiking activity of GABAergic neurons. We are now exploring the possibilities to express channelrhodopsin specifically in AVP neurons of the PVN in order to stimulate local AVP release in the VTA both in vitro and in vivo.

Optogenetic and electrophysiological dissection of oxytocin in brain circuits underlying social buffering of fear in male rats.

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Several studies have shown that the emotional state of a conspecific subject can influence one’s stress response. The attenuation of fear responses by the presence of a conspecific is called social buffering of fear (SBF), but the neural mechanisms underlying SBF are not yet fully understood. One candidate molecule to mediate SBF is oxytocin (OT), a neuropeptide well known for its pro-social effects. We previously found that activation of the OT receptors in the central amygdala (CeA) can significantly reduce expression of fear. We here focus on the understanding of the brain circuits which could mediate the endogenous release of OT, notably projections from the ParaVentricular Nucleus (PVN) of the hypothalamus to the CeA. We hypothesize that activation of these projections are important for the SBF response.

To test our hypothesis, we optogenetically or chemogenetically modulated endogenous release of OT after viral expression of the corresponding constructs under the promoter of OT, we pharmacologically activated or inactivated OT receptors, and we conducted electrophysiological recordings in vivo with optogenetic stimulation of the PVN-CeA pathway in rats all or not exposed to SBF.

We found that the presence of the conspecific immediately as well as long-lastingly decreased fear expression which was blocked by the local administration of an OT receptor antagonist. Electrophysiological recordings in vivo, in combination with optogenetic identification of OTergic neurons in the PVN, showed that these behavioral responses were accompanied by changes in the activity of neurons in the PVN as well as differential neuronal responses in the CeA depending on their sensitivity to OT. These findings aim to provide a first characterization of the OTergic circuits involved in SBF.

### Dynamic Regulation of Defensive Behavior by the Rodent and Human Basolateral Amygdala

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In response to a threat humans and many other mammals can respond passively by freezing or actively by goal-directed actions, such as fight or flight. Although substantial advances have been made in identifying regions and pathways in the rodent amygdala underlying passive threat responses, mechanisms involved in active escape and avoidance have been much less studied, and translation to the human amygdala remains altogether sparse. Here, in a comparative human-rodent study, we show that the basolateral region of the amygdala (BLA) promotes goal-directed escape over freezing behaviour in situations of imminent threat. We measured in five human subjects with selective bilateral damage in the basolateral amygdala (BLA) passive threat responses in a custom-designed threat-and-escape task (TET). In response to imminent, yet escapable threats, the BLA-damaged subjects showed, compared to healthy controls, an enhanced potentiation of the eye-blink startle response, a typical read-out of passive fear responses, but similar potentiation to distant or inescapable threats. Parallel fMRI measurements revealed simultaneous increased activation of the pons area in the brainstem and reduced functional crosstalk between pons and central amygdala (CeA).
To examine the precise roles of the BLA and CeA in this specific inhibition of passive responses to imminent-escapable threat in rodents, we developed a rat equivalent of the human TET and modulated these areas by chemogenetic and pharmacological intervention. Similar to BLA-lesioned human subjects exposed to imminent, yet escapable threat, chemogenetic inhibition of the BLA increased a potentiation of passive startle responses and furthermore, also increased freezing responses and decreased active escape. Pharmacological activation of a group of oxytocin-sensitive neurons in the lateral part of the central amygdala that is targeted by the BLA fully rescued these changes. Together, these cross-translational findings show how the BLA through the CeL may instrumentally control active versus passive responses to imminent threat when the possibility of escape is provided. The BLA could thus play, both in humans and rodents, an important role in preventing brainstem-generated defensive reflexes in situations of imminent threat, thus opening a window for successful goal-directed escape.

E20 Effects of Visual Richness on Context-dependent Memory

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Many theories of memory rely on a mechanism called context-dependent memory, which is consistent with the principle of encoding specificity (Tulving & Thomson, 1973). Context-dependent memory refers to the finding that learnt information can be recalled better when the context of the test setting matches the encoding setting, when compared to non-matching settings (e.g. Godden & Baddeley, 1975). Modulating the setting context can refer either to aspects of the physical environment (e.g. underwater vs. on land), sensory information (e.g. sounds), or even aspects of the person's internal state (e.g. mood) (Robertson et al., 2015). A popular method for manipulating environmental contexts in memory studies is the use of computer-generated or virtual environments. These contexts include aspects such as simple color cues, images, computer screen configurations, video recordings, or virtual reality devices (Smith, 2013). Here we ask whether the magnitude of the context-dependent memory effect depends on the richness of the visual context.

We conducted a series of experiments with different levels of visual richness. In Exp. 1, the visual context consisted background flickering during the encoding and recall of 24 German nouns. Words were presented to the participants on a computer screen with a grey background flickering at one of two indistinguishable frequencies and participants were asked to memorize the words. In the subsequent retrieval task, one of the two flicker frequencies was presented on the computer screen, while participants had to recall as many words as possible. Our main outcome measurement was whether words that were encoded with the same flicker frequency as during recall (congruent condition) could be recalled better compared to words that were encoded with the other flicker frequency (incongruent condition). First results indicate that there were no significant differences (p > 0.05) between congruent and incongruent conditions.

The goal of Exp. 2 was to replicate the findings of Isarida & Isarida (2007) by using two different background colors as the context cue. Unlike the background flickering, this type of contextual cues is clearly distinguishable. Using the same design as in Exp. 1, the memory performance of 30 participants was analyzed. We could not replicate the findings from Isarida & Isarida (2007). To the contrary, the data show a trend towards better memory performance for incongruent conditions compared to congruent conditions (p = 0.88).
In Exp. 3 participants were immersed in two different virtual environments via virtual reality glasses. The use of a head-mounted display allows the user dive into a computer-generated world with a unique sense of presence. This feeling, along with the 360-degree visual environment, was expected to lead to the strongest effect of context-dependent memory of the three experiments. First results will be presented at the conference.

Using various visual stimuli, we have not yet observed significant improvements when nouns are encoded and recalled in the same versus different contexts when tested at the group level. Initial results suggest that context-dependent memory effects are small and most likely vary among participants.

References


F. Computational and Theoretical Neuroscience

F1 Ohmic quasistatic models fail to describe the propagation of slow oscillations in the cortical network

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Models of the propagation of electromagnetic fields (LFP, EEG, MEG) in neural tissue presuppose the validity of
the quasistatic ohmic approximation (QSOA) of Maxwell equations. Upon this approximation, extensively applied in clinical (e.g. deep brain stimulation) and experimental neuroscience (e.g. current source density computation via Laplacian of Potentials), electromagnetic fields travel nearly instantaneously from the sources to the sensors. Yet, recent estimates of the propagation speed of epileptiform activity within hippocampal tissue are far too low (~0.1m/s) to justify quasistatics. We tested the assumptions of the QSOA by studying the propagation of slow wave oscillations (SWO) and epileptic activity in slices of visual cortex after isolating synaptic from electromagnetic transmission. Contrarily to the damped, undistorted instantaneous propagation of slow (<1Hz) waves and epileptic activity predicted by QSOA over short distances we observed substantial deformations and delays compatible with dispersion. Our results suggest that accurate macroscopic models of propagation of electromagnetic fields in neural tissue must consider the dispersive properties that account for the laminar and columnar cortical microstructure and that are determinant of macroscopic effective dielectric properties.

F2 The Neural Particle Filter as a Theory for Perception

Authors
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The robust estimation of dynamically changing features, such as the position of prey, is one of the hallmarks of perception. On an abstract, algorithmic level, nonlinear Bayesian filtering, i.e. the estimation of temporally changing signals based on the history of observations, provides a mathematical framework for dynamic perception in real time. Since the general, nonlinear filtering problem is analytically intractable, particle filters are considered among the most powerful approaches to approximating the solution numerically. Yet, these algorithms prevalently rely on importance weights, and thus it remains an unresolved question how the brain could implement such an inference strategy with a neuronal population. Here, we propose the Neural Particle Filter (NPF), a weight-less particle filter that can be interpreted as the neuronal dynamics of a recurrently connected neural network that receives feed-forward input from sensory neurons and represents the posterior probability distribution in terms of samples. Specifically, the NPF captures properties that are crucial for perception: 1) it relies on noisy and incomplete sensory data, 2) it uses prior knowledge of the dynamic structure of the environment, 3) it efficiently combines information from several sensory modalities, each with different levels of uncertainty, and 4) it can dynamically adapt to changes in the environment. Further, as an algorithm the NPF bridges the gap between the computational task of online state estimation and an implementation that allows networks of neurons in the brain to perform nonlinear Bayesian filtering. Numerically, the filtering performance of the NPF is comparable to that of a standard particle filter, and even exceeds it in high-dimensional models for a limited number of neurons.

F3 Machine Learning Classification of sensory neuroimaging data

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Neuroimaging could benefit strongly from Machine Learning methods in the recent years. We are specifically interested in the application of Machine Learning methods to neuroimaging data elicited during sensory stimulation, where we show first that easy-to-implement classification techniques can predict the stimulation of
different digits as well as predict different orders of digit stimulation. In a next step we investigate how well sensory perception of noisy data maps onto measures of classification performance such as classification accuracy, to later examine how these techniques can be employed for investigating changes in perceptive performance when prior information is provided before noisy sensory stimulation.

**F4**

**Modeling the interplay of thalamic firing properties and short-term plasticity at the thalamocortical synapse**

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How a cortical neuron responds to sensory stimuli is shaped by the activity of its thalamic afferents as well as the short-term dynamics at the thalamocortical (TC) synapses. TC synapses have been shown to be chronically depressed in vivo. However, a recent study revealed that even while being in a depressed state, TC synapses can undergo diverse forms of further short-term plasticity, including facilitation. It remains unclear how these complex synaptic dynamics affect the responses of the target cortical neurons. In this study, we used the NEURON simulation environment to investigate the response properties of cortical cells with different forms of synaptic organizations consistent with the observed synaptic diversity. Two scenarios were investigated - one in which all the TC synapses a given cell receives have the same dynamics (homogeneous synapse dynamics), and another scenario where they differ (heterogeneous synapse dynamics). We found that cells with homogeneous synapse dynamics could be differentially modulated not only by the average firing rate, but also by the temporal pattern of thalamic spike trains. Cells with heterogeneous synapse dynamics showed considerable differences in activity, depending on how well the dynamics of single synapses matched the average firing rates of single thalamic afferents. These results indicate that the short-term dynamics of TC synapses could modify the response properties of cortical cells with respect to information encoded in the temporal structure of thalamic spike trains. Our simulations suggest possible experiments that could lead to a better understanding of how TC synapse plasticity shapes cortical responses to sensory stimulation.

**F5**

**NEuromorphic implementation of a neural architecture for serial order memory**

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A neural-dynamic cognitive architecture for serial order memory can learn to store and reproduce actions and perceptual states. This architecture is based on the attractor dynamics of Dynamical Neural Fields and is implemented on a mixed-signal digital analogue neuromorphic hardware. Neuromorphic hardware realises networks of artificial spiking neurons with on-chip synaptic plasticity using analog electronic circuits to implement neural and synaptic dynamics with biologically plausible time constants. In this work we show how this architecture can be put in a closed behavioural loop using a robotic system. The neural network, implemented on neuromorphic hardware memorises a visual sequence perceived by the robot's neurally inspired camera DVS (dynamic vision sensor); the elements of the sequence are associated with actions, which the robot reproduces when it recalls the memorised sequence. The neuromorphic cognitive architecture is able to learn and forget sequences of different length in real-time. This work is a first robotic demonstration of the
The dynamics of reinforcement learning: repelled by aversive experiences or attracted by appetitive ones?

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Even in well-learned and precise motor tasks such as reaching or vocalizing, each repetition deviates slightly from the previous ones. It has been shown that this trial-by-trial variation is not only noise but it can effectively guide adaptive modifications of well-controlled and highly complex motor skills. While it is commonly accepted that variability is necessary for learning, it is currently unknown how exactly a single behavioral rendition shapes and improves future actions.

Birdsong learning provides a unique model system to study the neural systems underlying trial-and-error processes of reinforcement learning. Both spectral and temporal aspects of birdsong can be modified independently by delivering real-time auditory disruption as an aversive reinforcement to a subset of syllable renditions contingent on the trials' fundamental frequency (pitch) or duration (Ali et al., 2013).

We present dynamical system models to unravel the effect of a reinforced rendition on future renditions via the correlation between exploration and reward, as in the Williams model (Williams, 1992). From behavioral data in zebra finches and using the expectation maximization algorithm we are able to estimate crucial learning-related parameters such as the fraction of behavioral variance accessible for learning. Our model predicts that the maximum pitch shift a bird can learn increases linearly with the standard deviation of the pitch it produces. One of our goals is to estimate the influence of punished versus non-punished syllable renditions on future syllables, to disentangle their different roles in learning. We designed a new experiment to unravel whether birds learn by repeating non-punished syllable renditions or by avoiding the punished renditions.

A songbird-inspired spiking neural network model for sensorimotor sequence learning

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Sequences are ubiquitous in any kind of behaviour from communication to movements. Zebra finches learn a song consisting of several syllables at young age from a tutor and replay it later in a stereotyped manner. We present a spiking neural network model for learning sound sequences in a closed sensorimotor loop, inspired by bird song learning. The main building block of the model are dynamic neural fields (DNFs) implemented as spike-based winner-take-all networks (WTA).

On the sensory side of the model, a feature-based DNF representation of the sound is mapped to a 2D perceptual space using a spiking self-organizing map. On the motor side, sound is represented in a 2D field and generated using a model of the bird's vocal organ (Syrinx).

A mapping between the perceptual and the motor space is learned using STDP synapses. Sequences of sounds are acquired on two hierarchical levels:

(1) Each syllable in a song is represented as a trajectory in the sensory space that is mapped to an ordered population of chain neurons that creates a representation of time. Using auditory feedback, neurons of the
chain are then mapped to their corresponding motor representation; (2) A sequence of syllables is learned in a DNF-based serial order model. Overall, the model can learn to produce sounds and to reproduce the presented tutor sequences. We have tested our system on artificial stimuli so far and envision a neuromorphic closed-loop implementation.

G. Human Brain Imaging and Recording

G1  A nap to recap or how reward regulates hippocampal-prefrontal memory networks during daytime sleep in humans

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Sleep plays a crucial role in the consolidation of newly acquired memories. Yet, how our brain selects the noteworthy information that will be consolidated during sleep remains largely unknown. Here we show that post-learning sleep favors the selectivity of long-term consolidation: when tested three months after initial encoding, the most important (i.e., rewarded, strongly encoded) memories are better retained, and also remembered with higher subjective confidence. Our brain imaging data reveals that the functional interplay between dopaminergic reward regions, the prefrontal cortex and the hippocampus contributes to the integration of rewarded associative memories. We further show that sleep spindles strengthen memory representations based on reward values, suggesting a privileged replay of information yielding positive outcomes. These findings demonstrate that post-learning sleep determines the neural fate of motivationally-relevant memories and promotes a value-based stratification of long-term memory stores.

G2  New method for automatic surface-based segmentation of Heschl’s gyrus

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The goal of this project is to develop a novel computational morphometry method for the automatic segmentation of Heschl’s Gyrus (HG), considering possible multiple existing transverse temporal gyri (i.e. common stem and full posterior duplications). Existing software such as Freesurfer assigns duplications to the planum temporale (PT) (Destrieux et al, 2010), and makes a number of systematic labelling errors (PT label extends too far posteriorly, exclusion of medial portion of HG, errors in the case of common stem duplications). Our toolbox involves, for each subject and hemisphere, extracting three merged Freesurfer auditory cortex labels (Heschl’s gyrus, Heschl’s sulcus and the planum temporale from the Destrieux atlas), and automatic discarding of regions of the posterior Sylvian fissure/parietal operculum, curvature thresholding and then expansion of the surviving patches such as to recover the full extent of identified transverse temporal gyri. We validated this method by applying it to brain structural data in which we have previously shown relationships between auditory cortex volumes and phonetic learning (Golestani et al, 2007). We found that our toolbox indeed allows to achieve a somewhat higher correlation with phonetic learning scores that do HG volumes.
obtained using Freesurfer. We will further improve this method, and then use it to explore auditory cortex anatomy in the context of expertise and dysfunction.

G3 New method for automatic segmentation of Heschl’s Gyrus

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SSN Annual Meeting 1/19/17

G4 Resting state EEG activity as predictor of spatial working memory performance?

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Resting state EEG activity has been reported to predict IQ (Thatcher et al., 2005) and working memory performance (Kaminski et al., 2011) in healthy individuals. However, the link between brain spontaneous activity and specific cognitive functions has been sparsely investigated. In this study, we recorded resting state EEG from 17 healthy participants (7 young adults 25-30 years of age, M=27.29, SD=0.84; 10 older adults 64-75 years of age, M=70.50, SD=1.23) and tested them in a real world allocentric spatial memory task. We aimed to characterize an electrophysiological signature of the brain resting state activity, which could be used to predict spatial working memory performance in healthy individuals. Describing potential biomarkers of memory abilities will allow to further our understanding on the neurobiological basis and organization of human memory functions.
Brain networks underlying successful emotion regulation with real-time fMRI neurofeedback

Authors
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Introduction. Emotion regulation is an important aspect of our personal well-being and failure to regulate emotions has been associated with a variety of psychiatric disorders. Real-time fMRI based neurofeedback of brain areas that are involved in emotion processing such as the amygdala has been suggested as a viable training method to support people in improving their emotion regulation capabilities (Bruhl et al., 2014; Linden et al., 2012; Zotev et al., 2011). However, people differ in their ability to make use of neurofeedback for learning self-regulation of emotional brain areas. Here, we shed light on this heterogeneity by delineating the brain network that underlies learning successful self-regulation of the amygdala with the help of neurofeedback.

Methods. fMRI was performed on a 3T Philips Achieva scanner. Per run, 190 whole-brain EPI volumes were acquired (TR=2000ms, TE=25ms, 30 axial slices, 3×3×3 mm³ voxel size). 16 healthy participants took part in 4 neurofeedback training sessions spread over 4 weeks. In each session, participants performed ~3 training runs that consisted of blocks of viewing aversive IAPS images (VIEW) and blocks of regulating emotions induced by the aversive IAPS images using a cognitive reappraisal strategy (reality checking, REGULATE). Neurofeedback from the right amygdala was continuously presented using TurboBrainVoyager (v3.2.0) and following a protocol described in Caria et al. (2010). Regulation success was defined as the percentage of runs, where amygdala activation was lower during REGULATE compared to the VIEW condition. Offline data pre-processing comprised despiking, slice-timing correction, bias-field correction, realignment, non-linear transformation to MNI space (ANTs) and smoothing (6mm FWHM). GLM analyses and dynamic causal modeling (DCM) were performed in SPM12. The right amygdala and task active regions in the PFC were used in the model space. Functional connectivity, determined by the correlation of percent signal change during regulation blocks, was used to identify the task-relevant functional connections in the prefrontal cortex, which were used as priors for the DCM model space. The presence of prefrontal connections to and from the right amygdala were permuted to reflect the uncertainty about the regulatory input from PFC, resulting in 16 DCM models. TASK (i.e., VIEW+REGULATE) and REGULATE conditions were used as modulators on the prefrontal connections. TASK was used as driving input into V1 and modulators on the connections from V1.

Results. Using SPM analysis we observed more activation during passive viewing in the amygdala, dmPFC, vmPFC and other areas. REGULATE condition induced more activation in the preSMA and OFC. Functional connectivity analysis revealed significant positive correlations during REGULATE between dmPFC and rAmy, preSMA, OFC, and VMPFC as well as OFC and dmPFC and rAmy. Based on these results, a DCM model space was constructed to model effective connectivity in the prefrontal amygdala network. We found that regulation success was significantly positively correlated with endogenous connectivity (A) between dmPFC and vmPFC (forward: r=0.58 p=0.020, and backward: r=-0.54 p=0.033) and negatively correlated with modulation by REGULATE in dmPFC to preSMA (r=-0.52 p=0.040). Using BMA, we calculated two exploratory group models for the more and less successful half of the study population. We observed that amygdala down regulation by the dmPFC and OFC were only present in successful regulators.
Conclusion. Our findings provide new insights into the brain networks underlying successful neurofeedback training of amygdala activity in response to emotional stimuli. Using functional and effective connectivity analyses we were able to explain the observed heterogeneity in regulation success. This might help to identify more adequate targets for future neurofeedback studies, thus increasing the efficacy of this novel treatment option for affective disorders.

G6 tACS-fMRI reveals causal influence of power synchronized neural activity on resting fMRI connectivity

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Resting state fMRI (rs-fMRI) is commonly used to infer the brain’s intrinsic neural coupling, which exhibits specific spatiotemporal patterns in the form of resting state networks (RSNs). It has been hypothesized that slow rs-fMRI oscillations (<0.1 Hz) are driven by power fluctuations of electrophysiological rhythms that typically occur at much faster timescales (>5 Hz), however, causal evidence is currently lacking. Here we test this hypothesis by measuring rs-fMRI while transcranial alternating current stimulation (tACS) was used to apply two entrainment signals separately to left and right sensorimotor cortices. Each signal was tailored to the individual’s alpha rhythm (9-12 Hz) and fluctuated in amplitude according to a 1 Hz power envelope, thus mimicking the naturally occurring phase-amplitude coupling between alpha activity and the far slower delta rhythm. Interhemispheric coupling between the two entrainment signals was experimentally manipulated to synchronize either the power envelopes (power-synchronization) or the alpha phase (phase-synchronization).

EEG was acquired in 20 subjects. The individual alpha peak over motor areas (C3/C4) was measured, and the correlation and phase-relationship of the two signals and their envelopes was calculated. Next we used tACS to independently stimulate the two sensorimotor cortices at the individual alpha-frequency with either power-synchronized or phase-synchronized signals. Rs-fMRI was measured before, during and after the application of tACS. For each rs-fMRI measurement connectivity strength was quantified in the sensorimotor network using a dual regression approach and linear mixed effects models (L MEM).

The different tACS coupling modes resulted in significant differences in connectivity strength (L MEM, p=0.003). The application of power-synchronized tACS signals increased connectivity strength by 25±9%, which was significantly stronger than the effect of phase-synchronized tACS that led to a 8±7% increase (p=0.037). This effect outlasted the actual stimulation period with higher rs-fMRI connectivity after power-synchronized tACS (34±8% above baseline) than after phase-synchronized tACS (12±6%).

Our study demonstrates a causal relationship between the power synchronized coupling of neural rhythms and rs-fMRI connectivity, thus confirming one important mechanism linking fast neural rhythms to slow rs-fMRI oscillations. Moreover, our work introduces a new paradigm for modulating brain connectivity at rest which opens new avenues for fundamental research into the functional role of brain coupling modes, as well as for designing tACS signals to modulate long-range brain connectivity, for example, in patients with altered rs-fMRI connectivity.
Differentiating between Parkinson’s disease patients and healthy controls using quantitative EEG and neuropsychological tests

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Introduction: Quantitative EEG (QEEG) and neuropsychological parameters have been found to be associated with Parkinson’s disease (PD). We investigated the differences between PD patients and healthy controls (HC) in high-resolution QEEG and neuropsychological test measures to check for prediction accuracy and the most influential variables for the classification process.

Methods: High-resolution 256-channel EEG were recorded in 66 PD patients and 59 healthy controls. Neuropsychological assessment of the patients was done using 18 tests that covered five cognitive domains: attention, working memory, executive functions, memory and visuo-spatial functions. An average score for each domain was calculated along with an overall cognitive score, resulting in 6 additional scores. EEG data were processed to calculate the relative power in alpha, theta, delta, beta frequency bands across 10 regions of the brain. Alpha1/theta ratios were also calculated, resulting in a total of 77 QEEG frequency measures. Random Forest algorithm was applied to the data to check for prediction accuracy and to obtain variable importance plots.

Results: On combining the QEEG measures with all 24 available neuropsychological scores an AUC value of 0.88 was obtained along with a list of variables important for the classification process. Measures that were ranked higher in the list included the attention domain, overall cognitive score, beta frequency measures, followed by individual tests from the executive function and attention domain.

Conclusion: QEEG measures and neuropsychological measures are useful in distinguishing Parkinson’s disease patients from healthy controls with a considerable accuracy.
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Conclusion: QEEG measures and neuropsychological measures are useful in distinguishing Parkinson’s disease patients from healthy controls with a considerable accuracy.

G9  Mesial temporal EEG coherence but not HFO rate reflects workload of verbal working memory.

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Introduction: Working memory processing elicits workload-dependent theta oscillations in the human surface EEG [1] and high frequency oscillations (HFO ripples, >80 Hz) in rodent hippocampus, while HFO also serve as biomarkers of human epileptogenic tissue [2].

Methods: Four epilepsy patients performed a modified Sternberg task [1] while we recorded EEG on the scalp and in the mesial temporal lobe. We automatically detected HFO and analyzed EEG power and coherence during the task conditions fixation, stimulus encoding, and retention.

Results: Theta coherence between hippocampal recordings and surface EEG increased markedly with workload during retention in memory. While HFO evidenced the epileptogenic zone, neither HFO nor EEG power distinguished between task conditions or workload.

Conclusion: The task-dependent change in functional connectivity between cortex and hippocampus evidences the involvement of mesial temporal structures in the task. The value of HFO in determining the epileptogenic zone [2] was unaffected by cognitive processing.

H1. Disorders of the Nervous System: Basic mechanisms

Psychosocial stress leads to inflammation, altered dopamine function and impaired reward processing in mice

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The aetio-pathophysiology of impaired reward processing is poorly understood. According to the psycho-neuro-immune hypothesis, stress-induced immune-inflammation impacts on mesocorticolimbic dopamine (DA) function and disrupts the reward system. In mice, chronic social defeat (CSD) stress induced splenomegaly and increased splenic granulocytes, inflammatory monocytes and T helper 17 cells. CSD mice exhibited microglia activation in the ventral tegmental area (VTA). Interestingly, CSD led to activation of the kynurenine pathway, both in the periphery and in the VTA. In nucleus accumbens (NAcc), CSD mice showed decreased dopamine turnover (DOPAC/DA). Using GBR 12909, a potent DA transporter inhibitor, to increase synaptic DA, CSD mice exhibited attenuated hyper-locomotion and reduced NAcc early-immediate gene activation, indicative of impaired post-synaptic DA signalling. CSD mice demonstrated reduced reward processing in operant tests: they attained a lower ratio and less rewards in a progressive ratio schedule (PRS) test, and made less responses to an ambiguous stimulus in a learned non-reward (LNR) test. Neurotoxin DA depletion in VTA-NAcc induced these same operant deficits. This model provides support for a stress-inflammation-dopamine pathway underlying reward pathologies and will be used to identify novel targets for restoring adaptive DA function and reward processing.

H2. Molecular mechanisms of DAOA/G72 gene in human neuroblastoma cell lines

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Introduction: D-amino acid oxidase activator (DAOA)/G72, a risk gene in schizophrenia, is hypothesized to bind to D-amino acid oxidase (DAO) and modulate its activity. D-serine, a co-agonist of N-methyl-D-aspartate receptors (NMDAR) is oxidised by a flavoenzyme DAO in the brain. Thus, DAO can regulate the function of NMDAR via D-serine breakdown. One of the possible explanations for NMDAR hypofunction theory proposed in schizophrenia is probably increased activity of DAO leading to decreased D-serine. Since the effect of G72 on DAO is controversial, shown to both increase and decrease DAO activity, including modulation of mitochondrial function, our aim is to elucidate whether overexpressed G72 modulates DAO activity and furthermore neuronal
activity via NMDAR.

Methods: We transfected human neuroblastoma cell lines (SK-N-SH and SH-SY5Y) with LG72 construct and empty pEGFPN1 vector. The success of transfection was confirmed by GFP fluorescence, qRT-PCR, and Western blot which substantiated G72 mRNA and protein expression in transfected cells. We also stained the mitochondria in transfected cells with MitoTracker Red. DAO and NMDAR subunit 1 (NR1) protein expression in transfected cells was determined using Western blot.

Results and outlook: We found that there was a co-localisation of LG72 in the mitochondria of the transfected cells. The G72, DAO, and NR1 protein were detected in transfected cells at the expected sizes of 18 kDa, 40 kDa, and 120 kDa respectively. Experiments such as DAO activity assay and NMDAR activity using multi-electrode array technology (MEA) will be conducted to prove or disprove NMDAR hypofunction theory in vitro. These experiments will help in understanding interaction of G72 with DAO and NMDAR which can be potential pharmacological targets in schizophrenia treatment.

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**Functional and dynamic polymerization of the ALS-linked protein TDP-43 antagonizes its pathologic aggregation**

**Authors**

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**H3**

TDP-43 is a primarily nuclear RNA-binding protein (RBP), whose abnormal phosphorylation and cytoplasmic aggregation characterizes affected neurons in patients with amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD). Here, we report that physiological nuclear TDP-43 in mouse and human brain forms homo-oligomers that are resistant to cellular stress. Physiological TDP-43 oligomerization is mediated by its N-terminal domain (NTD), which can adopt dynamic, solenoid-like structures, as revealed by a 1.95 Å crystal structure in combination with nuclear magnetic resonance (NMR) spectroscopy and electron microscopy. These head-to-tail TDP-43 oligomers are unique among known RBPs and represent the functional form of the protein in vivo, since their destabilization resulted in loss of alternative splicing regulation of known neuronal RNA targets. Our findings indicate that NTD-driven oligomerization spatially separates the adjoining highly aggregation-prone, C-terminal low complexity domains (LCD) of consecutive TDP-43 monomers, thereby preventing LCD inter-molecular interactions and antagonizing the formation of pathologic aggregates.

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**Restoring cell surface expression of GABA (B) receptors: a potential strategy to limit neuronal death in cerebral ischemia**

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Cerebral ischemia is the leading cause for long-term disability and subsequent mortality in adults due to prolonged massive neuronal death. Major mechanism behind ischemia-induced neuronal death is the excessive release of glutamate upon oxygen and glucose deprivation (OGD) occurring during ischemic stroke. Ischemic
overexcitation of neurons downregulates GABA(B) receptors, which normally modulates excitatory neurotransmission by its slow and prolonged neuronal inhibition. Sustained activation of glutamate receptors increases the intracellular Ca2+ concentration enhancing the activity of CaMKII leading to the phosphorylation of GABAB receptors at S867 in the C-terminal domain of the GABAB1 subunit. This sorts the constitutively endocytosed GABAB receptors to lysosomal degradation instead of recycling them back to the cell surface. In this study we aim at observing the neuroprotective effects of restoring cell surface expression of GABAB receptors by interfering with the CaMKII-induced downregulation of GABAB receptors with short interfering peptides that prevent the interaction of CaMKII with GABAB1 subunit and consequently preventing the phosphorylation of GABAB1 (S867). Screening of short synthetic peptides homologous to the sequence of the GABAB1 C-terminal domain identified one peptide that prevented interaction of CaMKII with GABAB1 upon sustained activation of glutamate receptors. This short-interfering peptide prevented glutamate-induced downregulation of GABA(B) receptors in cultured cortical neurons and preserved cell surface levels of the receptors. Further, this peptide shows improved cell survival on glutamate treated cultured cortical neurons and OGD induced organotypic cortical slice cultures. We expect that the preserved cell surface GABAB receptors levels under ischemic conditions counteract the excessive neuronal excitation and thus limit neuronal death in-vivo.

H5  
Tau Modifications Associated to Specific Subcellular Locations

Hypothesis. Neurodegenerative diseases are lethal progressive disorders for which effective cures and early diagnostic measures are still missing. In these disorders, the gain-of-function role of proteotoxicity is defined by the existence of genetic mutations in proteins that form hallmark brain deposits whose distribution correlate with clinical symptoms. Proteotoxicity is explained by the acquisition of pathogenic protein conformations and post-translational modifications (PTMs). We have chosen the microtubule-associated protein tau as model protein to study proteinotoxicity. In pathological conditions, tau detaches from microtubule and redistribute from axon to somatodentritic compartment, impairing vesicular trafficking. Recent findings have shown tau also in the nucleus, where it contributes to maintain DNA integrity. Therefore, given these multiple subcellular locations, we hypothesize that subcellular location-specific PTMs of tau may explain its toxicity in disease.

Results. We implemented the split-GFP technology (Cabantous 2005 Nat. Biotech. 23, 102 – 107) to study location-specific PTMs of tau. GFP is split in two pieces, a large fragment named GFP1-10 and a small 16-aa peptide named S11. When the two parts co-localize they spontaneously reassemble and reconstitute GFP fluorescence. For our study, we tagged tau with S11 and produced GFP1-10 sensors restricted to specific cellular locations by fusion to targeting signals. This strategy allowed us firstly to detect with high sensitivity small pools of tau located to specific cellular locations also in living cells. Secondly, using the sensors as baits, we enriched for subcellular pools of tau allowing the characterization of location specific PTMs by ELISA and mass spectrometry. Ultimately, we plan to investigate the role of these newly discovered PTMs for tau proteotoxicity and disease progression.

Conclusions. The identification of location-specific PTMs of tau may lead to the identification of structural determinants of toxicity and to new markers of disease and disease progression.

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**H6** Neuronal activity-driven underpinnings of Alzheimer’s disease

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Alzheimer’s disease (AD) is an idiopathic neurodegenerative disease that progresses asymptomatically during decades and is belatedly diagnosed when therapeutic strategies are unavailable. A better understanding of earlier disease stages is thus crucial for developing more effective therapies against AD. Recent evidence points towards a direct causal relation between neuronal activity and amyloid pathology - the main hallmark of AD - although the mechanisms implicated are not well understood. We aim to investigate the relation between neuronal activity and amyloid formation at a hitherto unachieved cellular and molecular level. Using a combination of primary neuronal cultures, the APP/PS1 mouse model, and Designer Receptor Exclusively Activated by Designer Drugs (DREADD) viral constructs, we aim to activate and inactivate selected neuronal populations at desired times, and afterwards to investigate the formation of AD-related pathologies and their progression as well as the specific molecular alterations in these particular populations. Following this approach, we expect to gain mechanistic insights into the onset and progression of AD from a new angle, and to stimulate the development of more effective therapies for AD.

**H7** Evidence from Gene-Environment Mouse Models that Amygdala Oligodendropathy Contributes to Emotional Pathology

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Background: Oligodendrocyte (OL) function, most notably myelination, is essential for efficient functional connectivity within and between neurocircuits. In depression, expression of OL genes and proteins is attenuated, including in the amygdala. The aim of the present mouse study was to elucidate the role of oligodendrocytes in mediating stress-induced emotional pathologies.

Methods: Firstly, RNA-sequencing of the amygdala transcriptome and subsequent gene expression deconvolution (GED) analysis of these data were performed in mice that received 15 days of chronic social stress (CSS) and controls (CON). Based on these findings, a genetic mouse model of compromised OL function in terms of hemizygosity of the OL gene cyclic nucleotide phosphodiesterase (Cnp1) was utilised in a 2...
genotype (G) (WT, Cnp1+/-) x 2 environment (E) (CSS, CON) design, to study GxE effects on emotional behavior (social approach test, Pavlovian fear conditioning) and amygdala microglia activation (Iba-1 protein immunohistochemistry).

Results: CSS resulted in reduced expression of a number of OL-enriched genes in amygdala tissue and GED identified a decreased proportion of OLs in CSS mice. Interestingly, socio-sexual motivation was reduced in Cnp1+/- x CSS mice specifically; Cnp1+/- x CON mice exhibited impaired memory but Cnp1+/- x CSS mice nonetheless exhibited robust fear learning and memory. Iba-1 immunohistochemical analysis showed additive effects of GxE with microglia activation lowest in WT x CON and highest in Cnp1+/- x CSS mice.

Conclusions: This mouse-model study provides descriptive ExG and causal GxE evidence that reduced amygdala OL function is associated with inflammation and contributes to the pathophysiology via which CSS leads to emotional psychopathology.

H8 Molecules contributing to PKC-mediated reduction of dendritic growth in Purkinje cells

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Spinocerebellar Ataxia 14 (SCA14) is an autosomal-dominant disease leading to Purkinje cell dysfunction and degeneration in humans. Patients progressively develop difficulties of motor coordination especially affecting gait or speech. It has been shown that the disease can be caused by a point mutation in the PKC gene (S361G), which leads to activation of the kinase. Our lab has been working with transgenic mice expressing the mutated human PKC protein under a Purkinje cell specific promotor. Organotypic cerebellar slice cultures of these mice show a distinct Purkinje cell morphology with stunted and thickened dendrites closely resembling the morphology seen after pharmacological PKC activation. The mechanism of how increased PKC activity inhibits dendritic growth are however still unknown.

It is likely, that there are other molecules involved in the PKC-mediated effects and also that it is an imbalance of intracellular calcium levels ultimately manifesting in impaired dendritic development. We therefore performed affinity coupled mass spectrometry using cerebellar lysates purified for PKC to find potential interactors. Proteins found associated with PKC were then evaluated for expression, localization and function in Purkinje cells and few candidates selected for further investigation.

We are now aiming to elucidate the role of those candidates on Purkinje cell development as well as to characterize their interaction with PKC.

H9 Microglia in the rat subventricular zone remain activated after neonatal hypoxia-ischemia and support neurosphere generation in vitro

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Recent studies in rodents indicate that microglia in the subventricular zone (SVZ) support neurogenesis in
healthy newborn and after adult stroke. We characterized temporal changes in SVZ microglia after hypoxia-ischemia (HI) in rat neonates, and analyzed the effect of microglia depletion on neurosphere generation in vitro. Postnatal day (P) 7 rats were subjected to right-hemispheric (ipsilateral) HI or sham surgery and were sacrificed at P10, P20 or P40. Microglia were immunohistochemically analyzed in the anterior SVZ, the adjacent M2 cortex (CX) and median corpus callosum (CC). For a neurosphere assay, periventricular tissue including the ipsilateral SVZ from P10 sham or HI animals was dissociated and cultured. Microglia were selectively depleted in vitro by saporin-conjugated antibodies. Our results show that in sham ipsilateral SVZ, microglial density (Iba1+ cells per SVZ area) was constant between P10 and P40. The number of phagocytic microglia (ball-and-chain Iba1+ cells) and the ratio of activated microglia (CD68+Iba1+/Iba1+ cells) declined significantly after P10. However, in HI animals, microglial density and number of phagocytic microglia remained significantly increased until P40, and microglial activation until P20 respectively, when compared to age-matched sham SVZ. These findings were observed in the SVZ only and did not occur in the adjacent CX or CC. In periventricular cell cultures from both P10 sham and HI animals, neurosphere numbers were significantly reduced if microglia were depleted. To conclude, microglia in the postnatal SVZ undergo unique developmental phenotypic changes. While microglial activation rapidly decreases in sham SVZ, neonatal HI significantly alters microglial development with cell accumulation, prolonged phagocytosis and activation. Reduction of neurosphere numbers after microglia depletion in vitro suggests a supportive role of microglia for neurogenesis in early postnatal development and HI.

H10  Sustained activation of mTORC1 affects the integrity and function of the neuromuscular junction reminiscent of agerelated changes

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Aged skeletal muscle loses mass and function progressively, known as sarcopenia. In the sarcopenic muscle, the integrity of the neuromuscular junctions (NMJs) is also altered, characterized by their fragmentation. However, it is not known whether these structural alterations indeed affect the function of the NMJ and little is known of the mechanism involved. We recently reported that sustained activation of mammalian target of rapamycin complex 1 (mTORC1) results in muscle atrophy and weakness (Bentzinger and Lin et al, Skeletal Muscle. 2013, 3:6). Moreover, these mice (called TSCmKO mice) also showed impaired autophagy induction via the phosphorylation of ULK1 by active mTORC1 and a late onset myopathy (Castets and Lin et al, Cell Metab. 2013, 17:731). As those mice also show signs of precocious aging, we have now studied their NMJs. The postsynapses are fragmented in both fast-twitch EDL and slow-twitch soleus muscles of 2–month–old mice in comparison to those in control littermates. The 9–month–old TSCmKO mice show more severe fragmentation of postsynapses, indicating a progressive development of NMJ degeneration. To test the function of NMJs, we compared force generated in the soleus muscle by stimulating the nerve with that resulting from direct electrical stimulation of the muscle. While nerve- and direct stimulation resulted in the same force in control mice, nerve-stimulated tetanic force in 9–month, but not 2–month–old TSCmKO mice was significantly reduced to that by direct stimulation. Nevertheless, partial blockade of AChRs by d-tubocurarine showed that the safety factor of nerve-muscle transmission was already lower in 2–month–old TSCmKO mice compared to control littermates. These results indicate that sustained activation of mTORC1 affects the integrity and neurotransmission at the NMJ reminiscent of age-related changes, further adding support to the notion that alterations of mTOR signaling might be involved in the development of sarcopenia.
H11 Investigating the role of the serotonin receptor 3A in fear-related limbic brain oscillations

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In primates and rodents the serotonin system interacts with early-life stress (ELS) to modulate stress-related phenotypes. Recently, we found that in humans early life adversity affects the methylation of the serotonin 3a receptor (Htr3a) in an allele-specific manner (Perroud et al. 2016). The Htr3a is a cation selective ionotropic receptor specifically expressed in a subset of interneurons distributed in several limbic brain regions including the medial prefrontal cortex (mPFC), a region regulating fear behaviour. Recent findings in the field indicate that the firing of mPFC neuronal assembly is phase-locked with the ascending phase of 4Hz oscillations and coincides with defensive behaviors such as freezing (Dejean et al 2016). Htr3a-ko mice have previously been shown to display normal fear acquisition but fail to extinguish learned fear (Kondo et al 2013). Here, we first aimed to investigate the role of the Htr3a in mPFC oscillation during resting state. To do this, we performed intra-cortical electrophysiological recordings in head-fixed wild-type and Htr3a-ko mice and analyzed local field potentials in mPFC. Preliminary data indicate increased power in the theta range (4-8Hz) in the prelimbic mPFC of Htr3a-ko mice, suggesting a neuromodulatory role of Htr3a-mediated serotonin signaling on mPFC theta oscillations. Given these initial results, we aim to investigate the role Htr3a-dependent theta oscillations in fear extinction by implementing a behavioral fear paradigm in head-fix animals and monitoring correlates of fear response using pupillometry and intra-cortical local field potentials.

H12 Parvalbumin modulation: treatment for autism spectrum disorders?

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Autism spectrum disorders (ASD) consists of a group of neurodevelopmental disorders characterized by three core symptoms: impaired social interactions, communication deficits and stereotyped behavior. In post-mortem brains from autistic individuals and in different ASD mouse models, the numbers of immunoreactive interneurons positive for the expression of the calcium-binding protein parvalbumin (Pvalb neurons) were found to be decreased. We have demonstrated that in Shank mutant models this reduction was the result of parvalbumin (PV) protein down-regulation and not a loss of this interneuron subpopulation. The same held true for Pvalb mutant mice with reduced (PV+/-) or absent (PV-/-) PV expression; both genotypes showed an autistic-like phenotype. Since we hypothesized that PV-down-regulation might be sufficient to elicit the ASD-like traits, an upregulation of PV protein levels in PV-/- mice, possibly restoring them to wildtype levels, might diminish or possibly even abrogate the ASD-like phenotype. For these aims different strategies, including the production of transgenic mice with inducible up- and/or down-regulation of PV are generated. In one strain, the expression of PV can be reversibly blocked by an inducible shPvalb strategy. This allows for the testing whether the down-regulation of PV at a later (adult) stage will lead to an ASD-like phenotype in this transgenic line. Other strategies are focusing on re-expression and/ or upregulation of PV expression in PV-reduced (PV+/-) mice at selected time points. All mice with genetic and/or pharmacologic interventions will be tested at the
behavioral level including the sociability of mice in the 3-chamber test.

H13 Glycogen metabolism measured in the brain of insulin-resistant Goto-Kakizaki rats

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Diabetes impacts the central nervous system predisposing to cognitive decline. While glucose is the main source of energy fuelling the adult brain, brain glycogen is necessary for adequate neuronal function, for synaptic plasticity, and for learning and memory. In this study, we investigated glucose utilisation and glycogen metabolism in the brain of insulin-resistant Goto-Kakizaki (GK) and control Wistar rats by means of localised 13C magnetic resonance spectroscopy (MRS) during [1-13C]glucose infusion. Glucose metabolism was unaltered in GK rats relative to controls, as suggested by similar cerebral metabolic rate of glucose (CMRglc), apparent maximum transport rate (Tmax), and apparent Michaelis constant of glucose transport (Kt). Although glycogen concentration was similar, the rate labelling incorporation from [1-13C]glucose into glycogen was 0.24±0.05 and 0.48±0.09 µmol/g/h in GK and Wistar rats, respectively. This resulted in nearly doubled turnover time in GK rats relative to controls. In conclusion, we demonstrate that brain glycogen mobilisation is slower in insulin resistance despite normal brain glycogen content, which may have implications for the adequate support of neuronal function.

H14 A brain-penetrant 5-HT7 receptor agonist alleviates chronic pain behavior

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Neuropathic pain is a debilitating pathological condition. Irreversible peripheral and central sensitization is responsible for the establishment and maintenance of the painful condition. The Anterior Cingulate Cortex (ACC) is considered to play a central role in the processing of the emotional aspects of chronic pain. Changes in the neuronal activity in this brain area are causally linked to the development of neuropathic pain. We tested the influence of a new serotonin receptor (5-HT7R) agonist (LP-211) that crosses the blood-brain barrier on neuropathic pain. With electrophysiological and behavioral tests we quantified the modulatory effect of LP-211 in the ACC. We found that LP-211 recovered the resonance properties of layer 5 pyramidal neurons that were impaired in the neuropathic pain state. Acute i.p. injection of LP-211 had an antihyperalgesic effect, increasing the mechanical threshold in neuropathic pain animals that was partially explained by an action on the ACC. Finally, the acute treatment with LP-211 blocked the switch in the Place Escape/Avoidance Preference test in the animals affected by neuropathic pain. We conclude that a direct modulation of the ACC through the activation of 5-HT7 receptors dampens the emotional aspects of pain. Nevertheless, the systemic effect of LP-211 involves also other parts of the nociceptive system resulting in a substantial alleviation of the painful condition.
Context sensitization and memory account for ASD phenotypes in Shank3 -/-

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Autism spectrum disorder (ASD) is a group of neurodevelopmental disorders characterized by impaired social communication as well as repetitive and restricted behavioral patterns. Notably, patients typically avoid novel situations, and unexpected novelty aggravates symptoms.

Shank3 is a scaffolding protein at the postsynaptic density of glutamatergic synapses. SHANK3 deletion/mutations rank among the most prevalent genetic causes of autism, but how ASD symptoms are established and/or maintained in the absence of Shank3 has remained poorly understood.

Using Shank3-/- mice (Bidinosti et al., 2016), we here identify behavioral and circuit readouts analogous to human phenotypes that might be used in clinical trials to improve ASD symptoms in patients. In addition, we identify a sensitive period in early postnatal mice when application of Diazepam or Oxytocin receptor antagonist produces a long-lasting rescue of the behavioral and PV plasticity phenotypes in Shank3 mutant mice.

Shank3-/- mice exhibited normal familiar object recognition (FOR) and social behavior when initially exposed to a novel context. However, they failed to interact with objects or social cues specifically when re-exposed to that sensitized context on the next day or any time thereafter. Novel contexts that included familiar elements such as bedding did not produce interaction deficits. Repeated exposure to novelty through environmental enrichment produced a long-lasting rescue of context-associated interactions in Shank3 mutant mice. Our results suggest that context perception and memory, and not social skills might be at the core of ASD phenotypes.

Autologous neural cells ecosystem (ANCE) transplantation as therapy for Parkinson’s disease: a promising approach

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Parkinson’s disease (PD) is the 2nd most common neurodegenerative disease. Since the 70s, many laboratories explore dopamine neurons replacement as a therapeutic strategy in animal model of PD based on stem cell transplantations. Nevertheless, controversies regarding the use of stem cells (e.g. ethical and immune limitations) restrict their application. However, these limitations can be vanished by autologous cells transplantation. The present project aims to determine the impact of autologous neural cells ecosystem (ANCE) transplantation in four non-human primates (Macaca fasicularis) model of PD.

Before undergoing systemic parkinsonian lesions, the monkeys were trained to perform different motor tasks in order to define a baseline of motor performance for each monkey. According to the protocol developed by Brunet and colleagues (Bloch et al., 2014; Brunet et al., 2005; Brunet et al., 2002), small cortical biopsy was performed providing the cellular material needed for the transplantation. Moreover, during the entire
experiment, the dopaminergic state was evaluated with 18F-Dopa PET scan.

After the lesion, two monkeys showed severe motor symptoms, whereas the other two exhibited mild symptoms. Furthermore, a reduction about 80% of the 18F-Dopa striatal uptake was shown in three monkeys. These results were consistent with the number of dopamine neurons within the substantia nigra as well as the striatal density of dopamine projections.

Six months after the ANCE transplantations, all the monkeys presented significant improvement of their motor impairments (spontaneous activity, manual dexterity, posture, etc). This functional recovery was accompanied with an increase of 18F-Dopa striatal uptake.

Taken together these new data open new therapeutic perspectives for the ANCE approach regarding neurodegenerative disorders like Parkinson’s diseases.

H17 Microglia have a protective role in cerebral microvascular calcification in the mouse model for primary familial brain calcification.

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Primary familial brain calcification (PFBC) is a rare neurodegenerative disease, which exhibits an autosomal dominant inheritance. Clinical manifestations are variable (e.g. parkinsonism, dementia, psychosis), however, all patients present with bilateral brain calcifications in the basal ganglia. The pathogenic mechanism of PFBC is unknown, but several autopsy studies point to microvascular insufficiency. Although PFBC is a rare disease, brain calcifications are a common CT finding, and vascular dysfunction is the second cause of dementia after Alzheimer’s disease. Thus insights into PFBC will aid in better understanding vessel-associated calcification in the brain. Loss of function of platelet-derived growth factor-B (PDGFB) and its receptor, PDGFRB, are associated with PFBC, nonetheless the pathomechanism of vessel calcification due to their haploinsufficiency is not known. Previously we have shown that mouse PDGFB hypomorphs (Pdgfbret/ret) develop brain calcifications similar to PFBC patients and possess a strong pericyte-deficiency in the brain, as PDGFB/PDGFRB signaling pathway is crucial for pericyte recruitment to developing vessels. In this study, we have investigated the pathomechanism of cerebral microvascular calcification using Pdgfbret/ret mice. Current knowledge on PDGFB-PDGFR signaling steer to the idea that changes in the cellular constituents of the neurovascular unit modulate the formation of vessel-associated calcifications in the brain. In this project, the contribution of glia with special focus on microglia in microvessel calcification was investigated. We find evidence that microglia have a protective role in the microvascular mineralization in pdgfbret/ret mouse brains. Further studies are directed towards elucidating the mechanism behind the contribution of microglia to the development of vessel-associated calcification in the brain.
Protein complementation for the study of proteotoxicity in neurodegeneration

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Neurodegenerative disorders are highly debilitating diseases characterized by the presence of hallmark protein deposits in the brain. In disease, as a consequence of unknown reasons, these proteins undergo modifications and a conformational switch that triggers an aggregation cascade causing a gain of toxicity or a loss of physiological function. Oligomeric intermediates rather than amyloid deposits may represent the cause of neurotoxicity. However, the identification and classification of toxic oligomers is still under debate.

In order to understand more in depth this process, we implemented novel technologies facilitating the study of neurodegeneration-associated proteins in living cells. In fact, with the bipartite GFP complementation we analyze protein location within the cell, whereas with the tripartite GFP complementation we investigate protein-protein interactions. Beside these morphological studies, these techniques also allow for biochemical quantification and therefore analyze conditions able to modulate these potentially pathological processes. We validated this approach for the analysis of the nuclear oligomeric form of TDP-43, using as comparison the microtubule-associated protein tau. Genetic mutations in TDP-43 and tau cause fronto-temporal dementia.

We present the adaptation of protein complementation for the molecular characterization of multimeric assemblies of proteins causing neurodegenerative disorders.

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Tau modifications associated to specific subcellular locations

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Neurodegenerative diseases are lethal progressive disorders for which effective cures and early diagnostic measures are still missing. In these disorders, the gain-of-function role of proteotoxicity is defined by the existence of rare genetic mutations in proteins that form hallmark brain deposits whose distribution correlate with clinical symptoms. Proteotoxicity is explained by the acquisition of pathogenic protein conformations and post-translational modifications (PTMs). We have chosen the microtubule-associated protein tau as model protein to study proteinotoxicity. In pathological conditions, tau detaches from microtubule and redistribute from axon to somatodentritic compartment, impairing vesicular trafficking. Recent findings have shown tau also in the nucleus, where it contributes to maintain DNA integrity. Therefore, given these multiple subcellular locations, we hypothesize that subcellular location-specific PTMs of tau may explain its toxicity in disease.

We implemented the split-GFP technology (Cabantous 2005 Nat. Biotech. 23, 102 – 107) to study location-
specific PTMs of tau. For our study, we tagged tau with a short 16-aa peptide that complements the large, non-fluorescent fragment GFP1-10, which is restricted to specific cellular locations by fusion to targeting signals. This strategy allowed us firstly to detect with high sensitivity small pools of tau located to specific cellular locations in living cells. Secondly, using the sensors as baits, we enriched for subcellular pools of tau allowing the characterization of location specific PTMs by ELISA and mass spectrometry (in collaboration with the laboratory of Prof. Paola Picotti, Zurich). We plan now to investigate the role of these newly discovered PTMs for tau proteotoxicity and disease progression. The identification of location-specific PTMs of tau may lead to the identification of structural determinants of toxicity and to new markers of disease and disease progression.

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H20  Pathogenic Protein Spreading and Neurodegeneration

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The aim of our research is to reveal the role and mechanism of cell-to-cell spreading of potential toxic proteins in neurodegenerative disorders. In neurodegenerative diseases the nervous system gets progressively altered. Impaired structure and function, which is due to degeneration of neural cells, results in severe behavioral disabilities and often death of the patient. Well-known neurodegenerative diseases, like Alzheimer’s disease, Parkinson’s disease, Amyotrophic lateral sclerosis and Huntington’s disease are thought to be caused by an aberrant assembly of disease-specific proteins. These disorders are classified as Protein Misfolding Diseases (PMDs). Characteristic for most, if not all PMD’s, is that the decline of neural cells first occurs in a disease-specific brain region, but then progressively spreads through the brain following the neural connectivity pattern of the nervous system. Interestingly, recent evidence suggests that the misfolded proteins can propagate from one brain region to a functional connected brain region by transneuronal spreading. Therefore, the aim of our studies is to understand whether misfolded, toxic protein spreading in PMDs is a fundamental trigger for the onset and a key factor for the progression of neurodegeneration. We want to understand the role neuronal connectivity plays in this process and elucidate the underlying cellular/molecular pathways involved in the spreading of toxic proteins. Initially Huntington’s disease is used as a model disease, but the ultimate goal is to know whether toxic protein spreading is a disease pathway shared by many PMDs. We approach these questions by using a combination of genetic mouse models, human embryonic stem cell-derived neuronal cultures, molecular biology tools, imaging, optogenetics and electrophysiology to reveal:

- The relation between spreading and neuronal degeneration.
- The role neuronal connectivity plays in spreading.
- The cellular and molecular components borrowed by toxic proteins to transcellular (neuron-to-neuron, neuron-to-glia/astrocyte and vice versa) propagate.

This is done in state-of-the-art in vitro and in vivo experimental designs, including co-cultures of mouse organotypical brain slices with human stem cell-derived neurons to address disease specific questions in a human related context.

With this multidisciplinary approach we aim to disclose the mechanism of toxic protein spreading in order to possibly delay disease onset and / or slow down disease progression in Huntington’s disease and potentially in other neurodegenerative disorders.
H21  Synaptic dysfunction in early symptomatic stage in a mouse model of Huntington’s disease

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Huntington’s disease (HD) is an inherited, progressive neurodegenerative disorder characterized by motor, cognitive and psychiatric dysfunctions. The disease is caused by a mutation of the huntingtin (Htt) gene. Many symptoms of HD are associated to neuronal death of striatal neurons. However, this degeneration is preceded by synaptic dysfunctions, imbalance between glutamatergic and dopaminergic transmission onto striatal neurons. Here using the yeast artificial chromosome expressing the mutant Htt mouse model (YAC128) and cutting-edge techniques on electrophysiology associated with optogenetic tools, we characterize synaptic properties of glutamatergic transmission in an input specific manner onto medium spiny neurons (MSNs) of the dorsal striatum.

We found a decrease in the AMPA/NMDA ratio specifically at the corticostriatal synapses in MSNs at early symptomatic stage in YAC128 mice. In addition, preliminary data point toward an NMDAR transmission alteration at that specific synapses.

Identifying the mechanisms that regulate synaptic dysfunctions in a HD mouse model will help to design specific and targeted pharmacological interventions that could rescue and delay or even prevent the onset of the disease.

H22  Neuronal activity-driven underpinnings of Alzheimer’s disease

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Alzheimer’s disease (AD) is an idiopathic neurodegenerative disease that progresses asymptptomatically during decades and is belatedly diagnosed when therapeutic strategies are unavailable. A better understanding of earlier disease stages is thus crucial for developing more effective therapies against AD. Recent evidence points towards a direct causal relation between neuronal activity and amyloid pathology - the main hallmark of AD - although the mechanisms implicated are not well understood. Here, we propose to investigate the relation between neuronal activity and amyloid formation at a hitherto unachieved cellular and molecular level. Using a transgenic AD mouse model and several viral constructs, we will be able to activate and inactivate selected neuronal populations at desired times, and afterwards investigate the formation of AD-related pathologies and their progression as well as the specific molecular alterations in such particular populations. Following this approach, we expect to gain mechanistic insights into the onset and progression of AD from a new angle, and to stimulate the development of more effective therapies for AD.
H23  Neuronal activity-driven underpinnings of Alzheimer’s disease

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Alzheimer’s disease (AD) is an idiopathic neurodegenerative disease that progresses asymptptomatically during decades and is belatedly diagnosed when therapeutic strategies are unviable. A better understanding of earlier disease stages is thus crucial for developing more effective therapies against AD. Recent evidence points towards a direct causal relation between neuronal activity and amyloid pathology - the main hallmark of AD - although the mechanisms implicated are not well understood. Here, we propose to investigate the relation between neuronal activity and amyloid formation at a hitherto unachieved cellular and molecular level. Using a transgenic AD mouse model and several viral constructs, we will be able to activate and inactivate selected neuronal populations at desired times, and afterwards investigate the formation of AD-related pathologies and their progression as well as the specific molecular alterations in such particular populations. Following this approach, we expect to gain mechanistic insights into the onset and progression of AD from a new angle, and to stimulate the development of more effective therapies for AD.

H24  Molecules contributing to PKC-mediated reduction of dendritic growth in Purkinje cells

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Spinocerebellar Ataxia 14 (SCA14) is an autosomal-dominant disease leading to Purkinje cell dysfunction and degeneration in humans. Patients progressively develop difficulties of motor coordination especially affecting gait or speech. It has been shown that the disease can be caused by a point mutation in the PKC gene (S361G), which leads to activation of the kinase. Our lab has been working with transgenic mice expressing the mutated human PKC protein under a Purkinje cell specific promotor. Organotypic cerebellar slice cultures of these mice show a distinct Purkinje cell morphology with stunted and thickened dendrites closely resembling the morphology seen after pharmacological PKC activation. The mechanism of how increased PKC activity inhibits dendritic growth are however still unknown. It is likely, that there are other molecules involved in the PKC-mediated effects and also that it is an imbalance of intracellular calcium levels ultimately manifesting in impaired dendritic development. We therefore performed affinity coupled mass spectrometry using cerebellar lysates purified for PKC to find potential interactors. Proteins found associated with PKC were then evaluated for expression, localization and function in Purkinje cells and few candidates selected for further investigation. We are now aiming to elucidate the role of those candidates on Purkinje cell development as well as to characterize their interaction with PKC.
Prenatal VPA exposure differentially affects parvalbumin-expressing neurons in the cortex and striatum

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In utero exposure to the anti-epileptic drug valproic acid (VPA) has developed to a highly recognized model to study autism spectrum disorders (ASD) due to the given construct-, face- and predictive validity. Fast-spiking GABAergic interneurons expressing the slow-onset Ca2+ buffer parvalbumin (PV) were found to be lost/impaired in different ASD models and thus Pvalb neurons are likely to contribute to the pathophysiology of ASD. However, on the functional level, loss of Pvalb neurons and/or decreased expression of PV have different consequences. Therefore, we asked whether and to what extend PV interneurons are affected in VPA-exposed male C57Bl/6J mice.

Enhanced neuronal excitability and increased number of glutamatergic synapses promote network oscillations in a human stem cell-derived model of autism

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Valproic acid (VPA) is an anticonvulsant drug with histone deacetylase (HDAC) inhibition activity which is frequently used to treat epilepsy and bipolar disorders. VPA intake during pregnancy is associated with an increased risk of the unborn child to develop autism spectrum disorder (ASD). Using rodent models it could be shown that in utero VPA exposure results in an ASD-related behavioral phenotype in the offspring. On the neuronal level, alterations in both excitatory and inhibitory synaptic transmission as well as enhanced NMDA-mediated long-term potentiation have been proposed to contribute to these ASD phenotypes.

To investigate the effect of VPA on developing human neurons, we used hESC-derived human neural stem cells that can be differentiated into synaptically connected neuronal networks within 6 to 10 weeks. Neuronal cultures are treated with low concentrations of VPA (0.6 to 1 mM) throughout the entire differentiation process. We used whole-cell current-clamp and voltage-clamp recordings to study the maturation of passive and active membrane properties, miniature postsynaptic currents as well as spontaneous network activity, which revealed several important functional differences.

First, passive membrane properties were similar during early differentiation (2 weeks) but developed significantly slower with time in VPA treated neurons. At about 10 weeks, the input resistance was higher (1.44 ± 0.62 G versus 0.54 ± 0.3 G, P < 0.001, n =9, and 7) and the membrane capacitance was smaller than in control condition (50.1 ± 20.7 pF versus 102.3 ± 40 pF, P < 0.004, n = 8, and 9). In accordance with the increased input resistance, VPA treated neurons showed enhanced electrical excitability. Action potentials could be elicited by significantly smaller current pulses (10 ms) in VPA than in control neurons (163.3 ± 66.2 pA versus 442.9 ± 278.2 pA, P < 0.02, n = 6, and 7). Second, miniature excitatory postsynaptic currents (mEPSCs) in the presence of TTX and gabazine showed significantly higher frequency (1.46 ± 0.73 Hz vs. 0.52 ± 0.43 Hz, P < 0.02, n = 9, and 6) and amplitude (25.3 ± 3.8 pA vs. 17.4 ± 6.2 pA, P < 0.03, n = 9, and 6) in VPA treated neurons.
neurons compared to control neurons indicating enhanced formation of glutamatergic synapses upon VPA treatment. By contrast, frequency and amplitude of miniature GABAergic currents (mGPCs), measured in TTX, CNOX and AP5, were unchanged. Finally, we observed a strong increase in spontaneous synaptic activity in VPA treated networks. At about 6 to 7 weeks of differentiation ~83% of the VPA treated cultures (1 mM) showed rhythmic burst activity which could not be detected in control neurons at this developmental stage.

Taken together, our results indicate that early VPA exposure of human neurons during embryonic development leads to network hyperactivity, which is most likely generated by enhanced electrical excitability combined with a shift in synaptic excitation-inhibition balance. These mechanisms could substantially contribute to the increased ASD susceptibility upon in utero VPA exposure.

**H27**  
**Sustained activation of mTORC1 affects the integrity and function of the neuromuscular junction reminiscent of age-related changes**

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Aged skeletal muscle loses mass and function progressively, known as sarcopenia. In the sarcopenic muscle, the integrity of the neuromuscular junctions (NMJs) is also altered, characterized by their fragmentation. However, it is not known whether these structural alterations indeed affect the function of the NMJ and little is known of the mechanism involved. We recently reported that sustained activation of mammalian target of rapamycin complex 1 (mTORC1) results in muscle atrophy and weakness (Bentzinger and Lin et al, Skeletal Muscle. 2013, 3:6). Moreover, these mice (called TSCmKO mice) also showed impaired autophagy induction via the phosphorylation of ULK1 by active mTORC1 and a late onset myopathy (Castets and Lin et al, Cell Metab. 2013, 17:731). As those mice also show signs of precocious aging, we have now studied their NMJs. The postsynapses are fragmented in both fast-twitch EDL and slow-twitch soleus muscles of 2-month-old mice in comparison to those in control littermates. The 9-month-old TSCmKO mice show more severe fragmentation of postsynapses, indicating a progressive development of NMJ degeneration. To test the function of NMJs, we compared force generated in the soleus muscle by stimulating the nerve with that resulting from direct electrical stimulation of the muscle. While nerve- and direct stimulation resulted in the same force in control mice, nerve-stimulated tetanic force in 9-month, but not 2-month-old TSCmKO mice was significantly reduced to that by direct stimulation. Nevertheless, partial blockade of AChRs by d-tubocurarine showed that the safety factor of nerve-muscle transmission was already lower in 2-month-old TSCmKO mice compared to control littermates. These results indicate that sustained activation of mTORC1 affects the integrity and neurotransmission at the NMJ reminiscent of age-related changes, further adding support to the notion that alterations of mTOR signaling might be involved in the development of sarcopenia.

**H28**  
**Enhanced dopaminergic fiber outgrowth of grafts by antagonization of the Nogo-receptor 1 in a rat model of Parkinson’s disease**

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Transplantation of human fetal ventral mesencephalic dopaminergic neurons into the host brain is an experimental strategy for patients suffering from Parkinson’s disease. The success of this approach, however, is dependent on a number of parameters in the host brain including neurotrophic factors and growth inhibitors.
that interact with grafted dopaminergic neurons. While the potential of neurotrophic factors has been extensively investigated in this respect, repression of growth inhibitors has been basically neglected. Only recently, we demonstrated that the infusion of neutralizing antibodies against Nogo-A into the lateral ventricle of hemi-parkinsonian rats enhanced graft function. Since the Nogo-receptor 1 also interacts with other growth inhibitors in the brain, we aimed at investigating whether a direct antagonization of the receptor would result in even more robust effects. For that purpose hemi-parkinsonian rats were grafted with ventral mesencephalic tissue in combination with infusions of the Nogo-receptor 1 antagonist NEP1-40 into the lateral ventricles. Transplanted rats receiving saline infusions served as controls. Motor behavior using the cylinder test was assessed prior to the lesion as well as prior and one, three and five weeks after the transplantations. At the end of the experimental period number of graft-derived dopaminergic fibers growing into the host brain, number of surviving dopaminergic neurons and graft volume were analyzed. We observed that NEP1-40 treatment marginally but significantly enhanced graft-derived dopaminergic fiber outgrowth as compared to controls while no effects were detected for graft volume and survival of grafted dopaminergic neurons. Notably, the enhanced dopaminergic fiber outgrowth was not sufficient to induce an improved functional recovery as compared to controls. In sum, our findings demonstrate that antagonization of the Nogo-receptor 1 is inferior to neutralization of Nogo-A in supporting engraftment and functional recovery in an animal model of Parkinson’s disease.

H29 Organotypic hippocampal cultures subjected to oxygen-glucose deprivation as an in vitro model for ischemic brain damage induced by cardiac arrest

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Background:
Sudden cardiac arrest (CA) is the most important cause of global cerebral ischemia. Due to a lack of effective therapy to treat the subsequent brain damage, the majority of patients are left with incomplete neurological recovery. The aim of the present project is to develop an in vitro surrogate for the in vivo rat model of cardiac arrest/resuscitation, and use it to test the grafting of neuronal progenitor cells to mitigate the damage and/or enhance regeneration after ischemic brain injury induced by CA.

Methods:
Hippocampi are isolated from 6 days old Wistar rat pups and cut into 400m slices. Slices with intact morphology are cultivated on porous inserts for one week in serum-free medium. Organotypic hippocampal cultures are subjected to oxygen-glucose deprivation (OGD) to reproduce in vitro the ischemic brain damage observed in vivo after cardiac arrest. OGD is performed by transferring the cultures into glucose-free medium and incubating them in a sealed chamber with an oxygen-free atmosphere, achieved by flushing it with a 95%N2/5%CO2 gas mixture. Duration of the incubation is optimized to obtain damage similar to what is observed during cardiac arrest/resuscitation in the in vivo model. The extent of neuronal damage is quantified at different time points after OGD by Fluoro-Jade B (FJ) staining, specific for degenerating neurons. For the transplantation experiments, neuronal progenitor cells (NPCs) are isolated from hippocampi of newborn Wistar rats, taken into culture for one week and then grafted into injured cultures using a Hamilton syringe and a micromanipulator.

Results:
After testing different OGD incubation lengths, we identified 33 minutes as the time needed to damage the hippocampus to a similar extent as we observe in the in vivo model. Cresyl violet staining shows numerous
shrunken nuclei typical of dying neurons in the cornu ammonis field 1 (CA1) segment, known to be the most sensitive region of the hippocampus to ischemic damage. Quantification of FJ-positive cells confirmed that our OGD protocol induces a significantly higher amount of cell death in the CA1 segment compared to the normoxic control.

Immunohistochemical characterization of neurospheres derived from hippocampal cells isolated from newborn rats showed the presence of numerous nestin- and DCX-positive cells within the spheres.

After preliminary transplantations of chemically labelled cells obtained from dissociated neurospheres into injured hippocampal cultures, viable cells were found up to 5 days after grafting, confirming the overall feasibility of the procedure. Improvement of the injection procedure is currently performed.

Conclusion and outlook:
We could confirm that the CA1 neurons of the hippocampus are most susceptible to ischemic damage, validating this model as an in vitro surrogate for hippocampal damage induced by cardiac arrest/resuscitation. The immunohistochemical characterization of hippocampal cells-derived neurospheres confirmed their identity as neuronal progenitors and thereby their suitability for transplantation. After optimization of the NPC grafting into the damaged cultures, their survival, differentiation and integration in the neuronal network will be assessed. Several neuronal markers will be used to identify the degree of differentiation of the grafted cells: nestin and doublecortin (DCX) for stem- and progenitor cells, III-tubulin and microtubule-associated protein 2 (MAP2) for mature neurons and glial fibrillary acidic protein (GFAP) for astrocytes.

In future experiments we will use NPC isolated from GFP rats, facilitating the identification of the grafted cells. Once the method’s feasibility is demonstrated in vitro, we will apply the same treatment to the in vivo model of cardiac arrest/resuscitation and assess whether neuronal grafting leads to an improved neurofunctional outcome. This project represents the very first step in the development of a cell-based regenerative therapy after global cerebral ischemia consecutive to cardiac arrest.

H30 Neuroprotective Effect and Improved outcome in Bacterial meningitis by combination adjuvant therapy with Daptomycin, Doxycycline and Ceftriaxone

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Background
Bacterial meningitis is associated with high mortality and morbidity rates. An overshooting inflammatory reaction resulting from immune activation by bacterial components drives the pathophysiology leading to brain damage. Neurofunctional deficiencies resulting from damage to the central nervous system including hearing loss after meningitis are particularly detrimental during the period of learning and development in children. We aim to efficiently and synergistically target pathophysiological mechanisms responsible for brain damage in bacterial meningitis by combining adjunctive therapies previously shown to be neuroprotective when used as monotherapies.

Methods
Eleven day old Wister rats were infected intracisternally with 7.13 +/- 3.5 x 10^5 cfu/ml S.pneumoniae and randomized for treatment with a combination adjuvant therapy (n=72) consisting of daptomycin (10mg/kg, s.c., single application) plus ceftriaxone (100mg/kg, i.p. every 12 hours) plus doxycycline (30mg/kg, i.p. once daily
combined with ceftriaxone) or a monotherapy (n=72) with ceftriaxone (100mg, i.p., every 12 hours) plus saline (s.c., single application) in control animals. Cortical damage and hippocampal apoptosis were assessed histomorphometrically 42 hours after infection. Cytokine expression levels were analysed using a magnetic multiplexing system (Luminex Screening Assay, RD SystemsTM, Bio-Techne, USA). Three weeks after infection, evoked auditory potentials (ABR) were used to assess the hearing thresholds of the rats.

Results
At 42 hours after infection, combined adjuvant therapy with daptomycin plus doxycycline increased the survival rate from 62.7% in controls to 84.6% (log-rank p=0.007) and alleviated weight loss compared to controls (+1.0% weight gain with combination therapy vs 2.8% weight loss in monotherapy, p=0.002). The cortex of infected rats showed significantly less damage in the animals with the combined treatment regimen (1.2% vs 5.0% damage of total cortex volume, p=0.03). In addition, expression of the inflammatory cytokines IL-1beta, IL-6 and IL-10 were significantly reduced in the combined treatment group at either 8 or 24 hours after initiation of treatment. Animals treated with combined adjunctive therapy showed a trend towards better hearing capacity three weeks after the infection (median hearing threshold of 65dB vs 85dB in controls, p=0.089). Mild to moderately infected animals were protected from meningitis-induced hearing loss (median hearing threshold of 40dB vs 80dB in controls, p=0.048).

Conclusion
The combination therapy with the non-lytic antibiotic daptomycin and doxycycline with its inhibitory effect on microglia and matrix-metalloproteases (MMPs) showed to be both neuroprotective and otoprotective. These findings, together with the observed lower mortality identify the combination of adjuvant daptomycin with doxycycline as a promising therapeutic option to improve the outcome of bacterial meningitis.

H31 Elucidating the role of chaperones in prion biosynthesis and replication by siRNA mediated high-throughput screening

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Background
Prion diseases are transmissible neurodegenerative disorders fatally affecting humans and animals. The infectious agent is assumed to consist of the scrapie prion protein (PrPSc), a misfolded and aggregation-prone isoform of the cellular prion protein (PrPC). The molecular mechanisms behind PrPC biosynthesis and the conformational alterations from PrPC to PrPSc are still unknown. Chaperones can specifically prevent aggregation of aggregation-prone proteins by tight binding, unfold misfolded and aggregated proteins, and convert them into harmless native proteins or degraded peptides. We propose to identify chaperone genes that are involved in PrPC biosynthesis and PrPSc replication in mammalian cells.

Methods
We have established an RNAi high throughput screen (HTS) system that we will harness to knock down chaperone genes in neuroblastoma cells and subsequently measure PrPC or PrPSc by homogeneous phase fluorescence resonance energy transfer (HPFRET). Because chaperones collaborate with one or two co-chaperones, we plan to simultaneously knock down two or three chaperone genes. With our cell-based siRNA
HTS system on an acoustic dispensing platform and a robotic system cells are reversely transfected with small interfering RNAs (siRNAs) in 384 well plates and incubated for 72 hours. During incubation, the cell viability is assessed with RT-Glo. At the assay day, cells are lysed and PrPC or PrPSc signals are measured with HP-FRET. Experimental data and numerical and graphical quality controls are automatically pulled together in RMarkdown documents. After accomplishing PrPC and PrPSc screens in CAD5 cells, the findings are validated with other libraries or in other cell types generated by CRISPR-Cas9 genome editing.

Results
The PrPC single knockdown screen in CAD5 neuroblastoma cells was successfully completed. Calnexin and Calreticulin, which are ranked as hits, are involved in ER processing of glycoproteins and GPI-linked proteins, which both applies for the prion protein and gives us confidence in having found meaningful hits. Validation of other hits is ongoing. A PrPC double and triple knockdown screen will be performed soon. In order to gain mechanistic insight to PrPSc replication, we are currently establishing an automatized PrPSc screen.

Conclusion
Results of the PrPC single knockdown screen give evidence, that our RNAi HTS system provides an unbiased approach to identify chaperone genes involved in prion biosynthesis and replication.

H32 Rewrite or overwrite: Identification of neuronal circuits underlying the treatment of anxiety disorder

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Fear and other anxiety disorders develop after the experience of a traumatic event such as grave physical or psychological harm. Because of a strong emotional underpinning traumatic memories are extraordinarily robust and difficult to treat, evidenced by an estimated lifetime prevalence of close to 29%. Among the most efficacious treatments for anxiety disorders are exposure-based therapies, during which a patient is repeatedly confronted with the originally fear-eliciting stimulus in a safe environment so that the once fearful stimulus can be newly interpreted as neutral or safe. A fundamental element for successful exposure-based therapies is the reactivation of the traumatic memory, which initiates a time-limited process called memory reconsolidation, during which a memory becomes susceptible to disruption. However, the neurophysiological and molecular mechanisms underlying remote memory attenuation remain unclear.

In this project, we aim at unraveling the processes underlying remote memory attenuation. To this end, we are using an innovative combination of transgenic mice with direct in situ manipulations of neuronal subpopulations and cell type-specific transcriptomic and epigenetic profiling. Specifically, we inducibly and persistently tag neurons activated by remote memory recall, and subsequently capitalize on this tag threefold: First, by visualizing this tag after successful memory attenuation, we are identifying neuronal subpopulations that promote remote memory reduction. Second, by using this tag as an anchor for pharmacogenetic and optogenetic manipulations interfering with neuronal activity, we will determine a causal implication of these neurons in memory attenuation. Lastly, by employing this tag as bait, we will isolate neuronal subpopulations that promote memory attenuation to analyze their epigenetic regulation of gene expression, a core component of enduring forms of memories.
Marked changes of motor strategy in a complex manual dexterity task after permanent lesion of the primary motor cortex hand area assessed by chronic EMG recordings in non-human primate

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Precise quantification of motor function is necessary to test the efficiency of possible treatments enhancing functional recovery after CNS lesion such as stroke. In addition, manual dexterity and precision grip express the highly specialised feature of cortical motor control via the corticomotoneuronal system, specific to primates. We therefore analysed and compared the muscular pattern needed to perform a complex manual dexterity task before and after a permanent lesion of the hand representation of the primary motor cortex in non-human primate. To this aim, we analysed the electromyographic (EMG) activity of eight hand and arm muscles chronically implanted involved in the “reach and grasp” drawer task before and after micro-infusion of ibotenic acid in the hand representation of the primary motor cortex.

Preliminary analysis of rectified averaged EMG activities showed first a direct involvement of the forelimb muscles in the consecutive phases of the behavioural task (reaching phase, grasping phase and picking phase) following a proximo-distal temporal unfolding; second, the amplitude of EMG activity in distal and proximal muscles augmented with increasing levels of resistance opposing the drawer opening. After the cortical lesion, there was an acute phase of paralysis followed by a progressive though incomplete functional recovery reaching a plateau of performance after a few weeks. At plateau, we observed a dramatic decrease of EMG activity in the distal muscles reflecting a modification of the motor strategy consisting in a shift of EMG activity from the distal muscles, particularly affected by the permanent lesion, towards more proximal muscles. This experimental model of cortical lesion with chronic EMG recording allows, due to its stability, to monitor motor function in a complex behavioural task over months, and to quantify changes of muscular patterns after a permanent cortical lesion, including in the future assessment of possible effects of therapeutic strategies to enhance functional recovery.
The cortico-basal ganglia (BG)-thalamic loop is the circuit for motor control. The motor thalamus (MTh) represents the final structure of the BG since it receives direct projections from its output, i.e. the globus pallidus (GP) and substantia nigra reticulata (SNr). As the other thalamic nuclei, the MTh is characterized by glutamatergic neurons projecting to the cortex that are able to impose a permissive part on cortical activity. The reticular thalamus nucleus (RTn) exerts a strong modulatory feedback activity on the MTh, receiving glutamatergic afferents and sending back GABAergic projections. The interplay between these two structures is able to generate various types of cortical rhythmic activity such as slow wave sleep or pro-kinetic gamma oscillations.

It is well known that Parkinson’s disease (PD) is characterized by an aberrant synchronized lower beta activity but little is known about the generator of these “bad” oscillation. Since dopaminergic fibers from the substantia nigra pars compacta (SNC) have been shown on both the MTh and the nRT we aimed to characterize the impact of dopamine (DA) denervation on these two structures.

Methods
We investigated the firing properties of the MTh and the nRT cells with electrophysiological and biochemical methods, in chronic 6-hydroxydopamine (6-OHDA) DA depleted and in acutely DA-denervated animals in order to disentangle chronic compensatory mechanisms. For this purpose, we performed a tetrodotoxin (TTX)-mediated acute blockade of the SNC pathway on the MTh activity and we performed microdialysis analysis of the perfusates from the MTh during TTX injection.

Results
In PD animals we found a decreased activity of the MTh neurons and on the contrary the nRT neurons showed an increase of their firing rate. Of interest, only in the nRT neurons showed a change of their firing pattern with a different content of burst activity. Similar results were observed in the MTh after TTX injection, with a clear reduction and time-looked inhibition of the MTh cells and GABA increase.

Conclusion
The MTh is a structure strategically situated between BG and cortex. Its activity changes in DA depletion state confirming the classical scheme of BG functioning. Furthermore, the MTh is tightly modulated by the nRT that is affected by DA too.

I2 Targeting deregulated AMPK and mTORC1 pathways in DM1 improves muscle function via splicing-dependent and -independent mechanisms

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Myotonic Dystrophy type I (DM1) is a disabling multisystemic disease affecting skeletal muscle. The disease is caused by expanded (CTG)n repeats in the DMPK gene. RNA-hairpins formed by the elongated transcripts lead to sequestration of splicing factors, and thereby to mis-splicing of different genes. Although strategies have been tested to limit splicing defects, no causal treatment is available for the disease. Muscle atrophy in DM1 has been related to perturbation in catabolic processes, even though extensive investigations are lacking. Here, we investigated whether DM1-associated muscle alterations may be related to a deregulation of central metabolic signalling and/or of the autophagy process. We showed that muscles from HSALR mice, a well-

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characterized mouse model for DM1, maintain active mTORC1 signalling under starved conditions, while Akt is efficiently inhibited. Additionally, AMPK was not fully activated in muscle from starved mutant mice, which might be related to splicing-dependent CaMKII deficiency. Moreover, we observed that autophagy flux is impaired in HSALR muscle and in human DM1 myotubes, which may arise from the deregulation of AMPK/mTORC1 signalling. Most importantly, normalization of these pathways with pharmacological or dietary approaches potentially improved skeletal muscle strength and significantly reduced myotonia in HSALR mice. In particular, the AMPK agonist, AICAR, but not metformin, a drug known to induce the pathway, led to a striking amelioration of the relaxation time of mutant muscle, together with partial splicing correction. On the other hand, rapamycin, a mTORC1 inhibitor, and prolonged low-protein diet both reduced myotonia but not DM1-related mis-splicing, suggesting that alternative, splicing-independent mechanisms could improve muscle function in DM1. These findings highlight the involvement of AMPK/mTORC1 imbalance in DM1 muscle pathophysiology, and open new avenues regarding therapeutic options for the disease.

I3  Alpha-synuclein in skin biopsy is a potential biomarker of Parkinson’s Disease

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OBJECTIVES
The diagnosis of Parkinson’s disease (PD) lays on clinical signs of motor involvement that appear later on in the disease when most of the substantia nigra neurons are already lost. Hence, there is a need for a biomarker that can identify patients at the beginning of disease or at risk of developing PD. We aim to establish skin biopsies in PD as a specific method for identifying physiological and pathological forms of alpha-synuclein (a-syn) linked to the progression of the disease.

METHODS
We started a three year-longitudinal, observational, controlled study in which we collect clinical data and skin biopsy at three anatomical sites (ankle, thigh and cervical area) in patients with PD and age-matched healthy controls. Immunofluorescence and biochemical analysis of a-syn, phosphorylated a-syn and a-syn oligomers in skin nerves as well as intraepidermal nerve fiber density are assessed.

RESULTS
40 subjects have been enrolled so far. Preliminary results show that PD patients have significant differences in the amount of pathology-associated forms of a-syn in dermal nerves in comparison to healthy subjects. Furthermore, there is a significant axonal denervation in the cervical area which positively correlates to disease duration. Dermal denervation is stronger than epidermal nerve loss, in accordance to the localization of pathological a-syn deposits mainly in dermal autonomic structures.

CONCLUSIONS
A-syn detection in skin biopsy is an easily accessible biomarker for PD. Larger patient number and longer follow-up are needed to establish the specificity and sensitivity of the technique.
Targeting deregulated AMPK and mTORC1 pathways in DM1 improves muscle function via splicing-dependent and -independent mechanisms

Authors
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Myotonic Dystrophy type I (DM1) is a disabling multisystemic disease affecting skeletal muscle. The disease is caused by expanded (CTG)n repeats in the DMPK gene. RNA-hairpins formed by the elongated transcripts lead to sequestration of splicing factors, and thereby to mis-splicing of different genes. Although strategies have been tested to limit splicing defects, no causal treatment is available for the disease. Muscle atrophy in DM1 has been related to perturbation in catabolic processes, even though extensive investigations are lacking. Here, we investigated whether DM1-associated muscle alterations may be related to a deregulation of central metabolic signalling and/or of the autophagy process. We showed that muscles from HSALR mice, a well-characterized mouse model for DM1, maintain active mTORC1 signalling under starved conditions, while Akt is efficiently inhibited. Additionally, AMPK was not fully activated in muscle from starved mutant mice, which might be related to splicing-dependent CaMKII deficiency. Moreover, we observed that autophagy flux is impaired in HSALR muscle and in human DM1 myotubes, which may arise from the deregulation of AMPK/mTORC1 signalling. Most importantly, normalization of these pathways with pharmacological or dietary approaches potentially improved skeletal muscle strength and significantly reduced myotonia in HSALR mice. In particular, the AMPK agonist, AICAR, but not metformin, a drug known to induce the pathway, led to a striking amelioration of the relaxation time of mutant muscle, together with partial splicing correction. On the other hand, rapamycin, a mTORC1 inhibitor, and prolonged low-protein diet both reduced myotonia but not DM1-related mis-splicing, suggesting that alternative, splicing-independent mechanisms could improve muscle function in DM1. These findings highlight the involvement of AMPK/mTORC1 imbalance in DM1 muscle pathophysiology, and open new avenues regarding therapeutic options for the disease.

Cross-modal processing differentially affects attentional deployment in right-hemispheric patients with and without neglect

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Search tasks with cross-modal spatial cueing have been shown to improve healthy participants' search performance. However, the effects of such multisensory processing on the spatial deployment of attention in neurological patients with attentional disorders, particularly in patients with left-sided neglect, is not yet fully understood. This study investigated whether cross-modal cueing differentially affects attentional deployment in right-hemispheric patients with and without neglect. The results showed that cross-modal cueing enhanced search performance in patients without neglect, but not in those with neglect. Additionally, the study highlighted individual variability in the response to cross-modal processing, suggesting the need for individualized therapeutic approaches.

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understood. The aim of the present study was thus to investigate the effects of cross-modal spatial cueing on the performance in a visual search task in patients with right-hemispheric lesions, with and without left-sided neglect. Two groups of patients with right-hemispheric lesions (with and without left-sided neglect) and a group of age-matched healthy controls completed a search task with cross-modal spatial cueing, i.e., a visual search task with spatially congruent, incongruent, non-informative, and without auditory cues. To further assess participants’ accuracy in localizing the auditory cues, a unimodal sound localization task was also administered. Preliminary data analyses revealed that, in the unimodal visual search condition (i.e., without auditory cues), as expected neglect patients showed a worse performance for left- than right-sided targets. Additional auditory cues affected search performance exclusively in the left hemifield: spatial congruency improved search performance, incongruence deteriorated it, and spatially non-informative cues had no effect. Critically, patients’ sound localization accuracy modulated these effects, as indicated by the results of the control task. In healthy participants and in right-hemispheric patients without neglect, visual search performance was affected both in the left and the right hemifield. Yet, whereas healthy controls showed no left/right asymmetries in performance, such asymmetries emerged with the additional presentation of a congruent auditory cue in right-hemispheric patients without neglect. The findings of the present study demonstrate that multisensory processing differentially influences spatial attentional deployment in patients with right-hemispheric lesions with or without neglect: in neglect patients, congruent auditory cues decreased, and incongruent auditory cues increased attentional asymmetries; in right-hemispheric patients without neglect, congruent auditory cues led to the emergence of an attentional asymmetry. The results are thus also of potential relevance for neurorehabilitative trainings in patients with right-hemispheric lesions.

**I6 Neuroimaging biomarkers of tissue bridges and lesion area are potential outcome predictors after acute spinal cord injury**

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**Background:** In acute traumatic spinal cord injury (SCI), MRI following admission is of clinical value to characterize soft tissue damage and to determine the level and extent of injury, but limited for predicting neurological outcome. Moreover, the literature is void about the spatial and temporal macro-structural changes of cord damage itself and whether they hold potential for predicting clinical outcome.

**Objective:** To investigate spontaneous structural cervical cord damage in-vivo and its relationship with clinical outcomes at 1 year following acute traumatic cervical SCI.

**Methods:** Standard clinical MRI protocols (including axial/ sagittal T2-weighted images) provided data on structural changes at the epicenter of spinal cord lesions, including tissue bridges in 24 subacute tetraplegic patients, of which 13 were serially imaged over 1 year (1, 3, 6 and 12 months post injury). At the same time points, all patients were clinically assessed.

**Results:** Preserved midsagittal tissue bridges were identified in 20 patients and persisted in 13/13 patients while measures of lesion area and width decreased (p<0.05). Patients with midsagittal tissue bridges showed a distinct pattern of lower extremity evoked potentials and better clinical recovery. The extent of midsagittal tissue bridges and smaller lesions at 1 month predicted improved 1-year clinical recovery.

**Conclusion:** At about 4 weeks following acute SCI, MRI reliably captures anatomical changes at the lesion site.
that remain rather stable throughout the first year after injury. Both tissue bridges and the extent of damage are predictive of outcome at 1 year follow-up and could serve as neuroimaging biomarkers to validate the efficacy of regenerative therapies in the acute and chronic phase of injury.

I7 Resection of high frequency oscillations predicts seizure outcome in the individual patient

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Objective: High frequency oscillations (HFOs) are recognized as biomarkers for epileptogenic brain tissue. A remaining challenge for epilepsy surgery is the prospective classification of tissue sampled by individual electrode contacts.

Methods: We analysed long-term invasive recordings of 16 consecutive patients who subsequently underwent epilepsy surgery. HFOs were defined prospectively by a previously validated, automated algorithm and were detected separately in the ripple (80-250 Hz) and the fast ripple (FR, 250-500 Hz) frequencies. Contacts with the highest rate of ripples co-occurring with FR designated the HFO area.

Results: The HFO area was fully included in the resected area in all 11 patients who achieved seizure freedom (specificity 100%). The analysis of multiple intervals provided high reliability within and between nights for the individual patient. In 4 patients, the resected area included the HFO area, but seizures reoccurred (negative predictive value 73%). This may reflect the inherent limitations of electrode coverage or noncompliance in drug intake. The HFO area was only partially resected in the fifth patient suffering from recurrent seizures (positive predictive value 100%). Thus, the resection of the prospectively defined HFO area proved to be non-inferior to the surgical decision in all patients with seizure freedom, while it could have improved the outcome in one patient with recurrent seizures.

Conclusions: Using a fully automated algorithm, we validated the clinical relevance of the HFO area in the individual patient. This is a prerequisite before HFOs can guide surgical treatment in multicentre studies.