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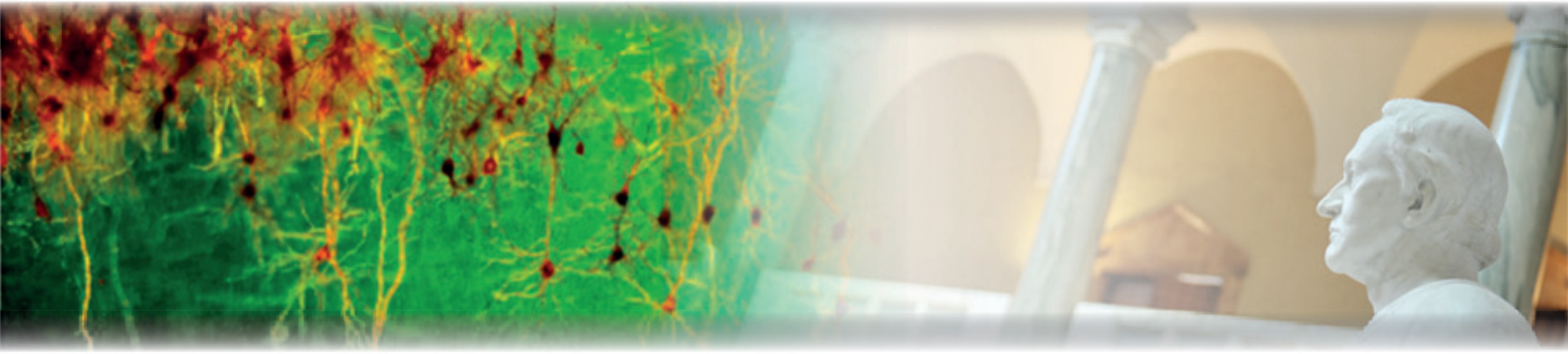

Poster Session
Abstract Booklet for the GSN Orientation Week 2014

Contents

Unraveling the Interplay between Spatial Navigation and Value-based Decision Making Strategies in Humans

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Studies on spatial navigation in humans have reported that the brain relies on two complimentary strategies to find way in large-scale novel environments by employing either route-based or map based navigation [1], [2]. Similar dual strategy approach exist for value-based decision making where subjects utilize either a model-free, which relies on repetition of successful behavior, or model-based approach to search for a set of actions within a decision tree that will lead to desired outcomes [3]. Recent neuroimaging studies have provided direct evidence that these two decision making strategies operate independently as well as in parallel and recruit neural structures along a medio lateral axis in basal ganglia [4].

In this study, we investigate whether egocentric cues can encourage subjects to use certain strategy during specific trials and how the observed results can be explained by reinforcement learning model. Thus the core of our navigation experiment is a grid

world task where the subjects can navigate in a virtual environment with connected rooms in order to find specific objects. Different grid sizes and transitions between neighboring rooms are employed in designing the experiment. We examine (1) the possibility of using spatial navigation paradigm in studying value-based decision-making in humans and (2) the possibility of finding common mechanisms and correlation of strategies in spatial navigation and value-based decision making.

Our results show that the subjects are able to utilize the provided cues to navigate and find optimal path to reach certain objects. This indicates that the behavioral task serves as a suitable experimental paradigm to observe process of learning. Computational model is then developed based on several reinforcement learning algorithms. It is desired to find the most suitable algorithm that lead to simple but powerful models that can best predict the subjects' choice behavior.

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Secondary-task effects in contextual cueing of visual search

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Repetition of display arrangement enables faster visual search, an effect known as implicit contextual cueing (Chun & Jiang, 1998). While it is accepted that the cueing effect aids attention (Johnson et al., 2007; Geyer et al., 2010), more recent investigations have asked the opposite question, namely, whether contextual cueing itself is affected by attention, both in terms of selectivity and processing resources deployed (Jiang & Leung, 2005). On one hand it was found that contextual cueing is unaffected by divided attention, i.e., a secondary working memory (WM) task (Vickery et al 2010). On the other hand, studies that did more carefully control for the effects of the secondary task in the learning vs. expression of learning found that particularly the latter process, of the retrieval of contextual information from long-term memory (LTM), is hampered by the secondary WM task (Manginelli et al, 2013). Findings along these lines suggest that WM provides a workspace between LTM and visual search (Annac et al, 2013). Occupying this workspace by a secondary WM task impedes the expression of learned contextual associations from LTM.

The present experiment further tested the hypothesis that WM influences the retrieval of contextual cueing from LTM by the novel manipulation of alternating between pure search and search + WM blocks. The prediction was that of the presence vs. absence of the cueing effect in pure search and search + WM blocks, respectively. Interestingly, contextual cueing became manifest in both types of blocks. However, the onset of the cueing effect was delayed in search + WM relative to pure search blocks. We take the results to mean that the retrieval of contextual cueing can be supported by both a direct WM route (Annac et al., 2013), and a more indirect route bypassing WM (present investigation).

Role of HDAC9 in atherosclerosis and stroke

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Background and Purpose:

In a recent genome-wide association study for ischemic stroke the so far strongest risk locus for large vessel (atherosclerotic) stroke was identified in the chromosome 7p21.1 region. This locus overlaps with the tail end of the HDAC9 gene, a histone deacetylase with an established function in inflammatory processes. HDAC9 mRNA levels were found to be elevated in peripheral blood mononuclear cells of healthy risk allele carriers. These findings make HDAC9 a promising candidate gene for atherosclerosis and stroke. In this study we investigated the consequences of HDAC9 deficiency on atherosclerosis and on ischemic stroke outcome.

Results:

We used ApoE deficient mice (ApoE-/-) as a model for atherosclerosis and the transient middle cerebral artery occlusion (tMCAo) as a model for ischemic stroke. Compared to $HDAC9^{+/+}ApoE^{-/-}$ mice, $HDAC9^{-/-}ApoE^{-/-}$ mice exhibited markedly reduced lesion sizes and significantly less advanced lesions throughout atherosclerotic aortas. In contrast to the protective effect of HDAC9 deficiency in atherosclerosis, $HDAC9^{-/-}$ mice had increased infarct volumes and more severe neurological deficits after tMCAo.

Conclusion:

Pharmacological inhibition of HDAC9 may be a potential strategy to prevent atherosclerosis, but not to improve ischemic stroke outcome.

Corollary discharge to trigeminal motoneurons couples two motor behaviours

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Movements have sensory consequences – corollary discharge is a mechanism that deals with these consequences by informing the sensory systems about the impending movements, reducing reafference or distinguishing self-generated from external sensory inputs. However, rhythmic locomotion not only affects sensory systems but also influences other motor behaviours such as respiration or eye movements, possibly via corollary discharge. Here we describe an example of such a corollary discharge that has motor consequences, and which targets trigeminal motoneurons. Tadpoles of *Xenopus laevis* have their tentacles, rod-like paired appendages at the corners of the mouth, which are thought to serve a mechanoreceptive role. These are retracted during swimming. Using video tracking, we quantified the pattern of tentacle movement in a reduced head-fixed *Xenopus* preparation during fictive locomotion. Anatomical experiments confirmed the trigeminal innervation of the tentacle muscle and showed that these motor neurons form a specific cluster in the hindbrain. Multi-unit recordings of trigeminal neurons showed tonic discharges during fictive swimming in the nerve branch that innervates the tentacle muscle, with the duration of

the activity closely matching the duration of swimming. Moreover, movement of the tentacle and activity in these trigeminal neurons occurred more often with high- than low-amplitude swimming. Some trigeminal neurons phase-locked to the swimming pattern, suggesting that they receive input from spinal central pattern generators. We hypothesize that the retraction of the tentacles during swimming diminishes reafferent stimulation of the touch-receptive Merkel cells on the tentacles in addition to reducing hydrodynamic drag.

A novel cell-culture model to study interaction of proteins with implication in neurodegenerative diseases

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The deposition and oligomerisation of proteins is a common hallmark of several neurodegenerative disorders including Alzheimer's disease (AD) and Parkinson´s disease (PD). Lines of evidence point towards a causal implication of this oligomerisation on disease progression. Hence, modulating the interaction of such proteins holds high potential as a therapeutic target.

We here develop stable cell lines that inducibly express proteins associated with neurodegeneration. Interaction of these proteins can be investigated via bimolecular fluorescence complementation (BiFC). For this, protein constructs were subcloned into lentiviral expression plasmids behind an UAS-sequence. Lentiviruses of these constructs and a driver-virus expressing Gal4 (for constitutive transgene expression) or Gal4 coupled to an ecdysone-receptor (Gal4-EcR; for inducible transgene expression) were produced and stable H4 and LUHMES cell lines were established.

Expression of the transgene in the inducible system can be initiated by addition of Tebufenozide.

We found that both H4 and LUHMES cells were susceptible to viral transduction. Following virus transduction we obtained transgene expression in up to 98% of cells with the fraction of transgene expressing cells being stable for at least two weeks. In the inducible system, expression of transgenes in the absence of Tebufenozide was low and increased over several magnitudes following incubation with the agonist. Using the BiFC-system we could monitor interaction of proteins with implication in neurodegenerative diseases (like α-Synuclein or Tau) and the influence of incubation with known modulators of α-Synuclein aggregation (Baicalein, anle138b, anle138c).

Magnetic Vestibular Stimulation (MVS) influences fMRI resting-state fluctuations
The modulation of the default-mode network as an exemplary case

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Dizziness in the presence of strong magnetic fields has been noticed ever since the first magnetic resonance experiments at high field strengths (>1Tesla) have been conducted. It was suggested that this was due to the changing magnetic flux in the inner ear induced by the gross subject-motion within the magnetic field and that the motionless presence in the static field of a MRI could not affect subjects significantly (e.g. [Schenck JF Ann.NYAcad.Sci. 1992]). Recently however, Roberts et al. [CurrBiol 2011] showed that Subjects at rest who are kept in total darkness and exposed to the static magnetic field of an MRI developed a persistent Nystagmus that did not stop as long as subjects were exposed to the field, even when Subjects remained motionless. This Nystagmus' slow phase velocity was modulated systematically depending on the subject's head orientation relative to the field, even while Subjects remained motionless. They argued that the ionic fluids in the inner ear, which are constantly

flowing as cells maintain resting activity, will be diverted by a (magnetic) Lorentz-force and this creates a pressure onto the Cupula "the rotatory motion sensor" in the inner ear, thus leading to a Nystagmus akin to a constant (accelerating) rotatory stimulation. This model is further supported by a simulation study by Antunes et al. [Phys.Med.Biol. 2012] and a recent study of patients with unilateral labyrinthine disorders by Ward et al. [Front.Neurol. 2014].

It was speculated that this magnetic vestibular stimulation (MVS) effect might influence fMRI results, given that a Nystagmus is an indication for the vestibular system not being in equilibrium.

The aim of our study was to replicate the behavioral results of Roberts et al. [CurrBiol 2011] and investigate if this MVS effect does indeed modulate the fluctuations of fMRI responses.

Here we treat the case of MVS influencing resting-state networks, presenting results from resting-state experiments conducted at two different field strengths (1.5Tesla & 3Tesla) and focus in particular on the influence that MVS has on the default mode network. We will show that those subparts of the default mode network that are significantly modulated between field strengths are also commonly associated with vestibular functions and furthermore, that the scaling behavior of these subparts is different from the other parts of the default mode network that are not significantly modulated. I.e. the scaling behavior is in agreement with a modulation due to MVS as expected from a Lorentz-model perspective (i.e. linear increase) while the other parts that are not significantly modulated by the MVS effect show a scaling behavior that is expected simply from considering fMRI signal scaling behavior due to increased field

strength (i.e. approximately the square root of the field strength, e.g. see [Duyn NeuroImage 2012]).

Aging and the Neuronal Correlates of Tool Use and Action Planning

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Introduction:

The use of tools is an essential aspect of our daily routine, which we encounter during our whole lifespan. Several studies deal with the neuronal processes of tool use, but mostly analyze young adults. A neuronal effect of aging in the motor domain was found in studies focusing on simple hand movements. The question if the neuronal processes of a complex action like the manipulation of tools changes in elderly adults is yet unclear. The goal of this study is to examine the neuronal processes of actual tool use with functional magnetic resonance imaging (fMRI) under utmost realistic conditions and focus on the influence of age on this process.

Methods.

Seventeen young (mean age 24.95 years; standard deviation 2.06 years) and seventeen elderly subjects (mean age 67 years; standard deviation 6.88 years) were tested in this fMRI study. With the help of a special apparatus, which was installed above the hip of

the subjects in the MRI scanner, real objects (tools and unknown objects) could be presented to the participants. In the data analysis, the effect of age during planning and execution of real actions with the objects was of most interest.

Results:

Besides a left-sided lateralization, a wide spread network (including frontal, parietal and temporal centers) can be identified, which is specific for processing complex tool related actions in both young and elderly subjects. The comparison between both age groups shows that the main structure of the tool network is stable across age, but strongly differs in activation strength in both phases of the action. A difference can be seen in the elderly subjects, who recruit a wider and less focused network during action planning but a smaller, weaker activation pattern during actual action execution.

Conclusions:

Impaired motoric actions like the use of tools can be the result of brain lesions after a stroke and is seen in patients with apraxia. In order to understand the neuroanatomical correlates of apraxia it is important to know the neuronal networks of complex actions like tool use in an age-matched population. The recruitment of a wider network in elderly might either be necessary to compensate for possible neurodegenerative effects or might be due to a general dedifferentiation of neuronal networks. Our results suggest that core regions of the neural tool use network largely maintain their function in older age, but the strength and size of recruitment differs during the different stages of the action.

Local postsynaptic sodium channel activation in dendritic spines of olfactory bulb granule cells

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Recent findings imply that spines can operate both as chemical and electrical compartments in which voltge-gated conductances can be activated locally. Here we provide direct evidence for postsynaptic voltage dependent sodium channel (Na_v) activation localized within spines.

The olfactory bulb (OB) granule cell (GC)/mitral cell reciprocal synapse is a special dendrodendritic connection. On the GC side, it consists of a glutamatergic postsynapse and a GABAergic presynapse within the same spine. By means of two-photon glutamate uncaging (TPU) we could directly stimulate individual GC spines in acute OB brain slices from juvenile Wistar rats (P11 – 17) while reading out local calcium signals as $(\Delta F/F)_{TPU}$ via two-photon imaging and recording uncaging-evoked EPSPs (uEPSPs) at the soma.

Physiological TPU stimulation levels were assessed by comparing $(\Delta F/F)_{TPU}$ and uEPSPs with previously recorded synaptic data. Again, TPU-evoked $Ca2^+$ transients were strictly localized to single spine heads and also otherwise showed similar properties, as well as uEPSPs.

Blocking Na_vs with 500 nM TTX resulted in a strong reduction of $(\Delta F/F)_{TPU}$ in most spines (to 0.63 ± 0.20 of control, mean ± S.D., n = 35). uEPSP amplitudes were slightly decreased (0.88 ± 0.30 of control) whereas the rise time became substantially slower (1.24 ± 0.37 of control). Notably, across experiments the magnitude of the blocking effect of TTX on $(\Delta F/F)_{TPU}$ was highly correlated with the magnitude of the TTX-induced increase in rise time (r = - 0.72). We hypothesized that the extra depolarization provided by Na_vs boosts $Ca2^+$ entry mainly via high voltage activated calcium channels (HVACCs).Thus we blocked N/P/Q type $Ca2^+$ channels with ω-conotoxin MVIIC (CTX), which decreased $(\Delta F/F)_{TPU}$ to 0.67 ± 0.19 of control (n= 24). CTX applied after TTX reduced $(\Delta F/F)_{TPU}$ only marginally (to 0.88 ± 0.22 of TTX-only condition, n = 14). The reverse experiment (TTX after CTX) yielded 0.97 ± 0.22 vs. CTX-only (n =8). Thus HVACC activation is the main source of Na_v-induced $Ca2^+$ entry.

Our results strongly suggest that Na_vs contribute to local postsynaptic $Ca2^+$ entry through HVACC activation, adding yet another crucial postsynaptic conductance to the GC spine's tool kit for its operation as an independent microcircuit. The observed acceleration of EPSPs by Na_vs may contribute to precise timing of GC output, e.g. in the context of fast sensory-evoked network oscillations.

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Modulation of the proliferative response of cortical astrocytes reacting to stab wound injury in the adult mouse brain

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Astrocytes are a multifaceted type of cells in the central nervous system that exhibit a remarkable range of critical functions, including regulation of neural network activity and maintenance of tissue homeostasis. At the earliest stages of development, astroglial cells act as multipotent neural stem cells and a limited number of them retain their proliferative and neurogenic potentials throughout adult life, contributing to adult neurogenesis in the neurogenic niches – the subependymal zone of the lateral ventricle and the subgranular zone of the dentate gyrus. Although astrocytes in the healthy adult brain do not proliferate outside these niches, acute invasive injury triggers both proliferation and activation of stem cell potential in a subpopulation of reactive parenchymal astrocytes (Buffo *et al.*, 2008; Sirko *et al.*, 2013; Dimou and Götz, 2014). The occurrence of proliferating astrocytes within living injured brain parenchyma (Bardehle *et al.*, 2013) suggests that pathological stimuli could elicit a certain degree of plasticity in mature parenchymal astrocytes, which may be particularly valuable for endogenous repair in the injured adult brain. Given that only a

limited subset of reactive astrocytes in the injured cortical parenchyma are prone to undergo a single cell division *in vivo* (Bardehle *et al*., 2013), the aim of this study was to assess whether and to which extent the proliferative response of cortical reactive astrocytes could be modulated by repetitive exposure to pathological stimuli. To address this question, we analyzed the acquisition of cycling activity of reactive astrocytes through their response to a repetitive pathological event in the cerebral cortex. For this purpose, we used a dual-labeling method to tag cycling cells during S-phase *in vivo* by combining two thymidine analogs, 5-bromo-2'-deoxyuridine (BrdU) and 5-ethynyl-2'-deoxyuridine (EdU) at different time points after stab wound injury. Quantitative analysis of *in vivo*-labeled cells shows that repetitive pathological stimuli lead to an expansion of the proliferative pool of reactive astrocytes, which occurs hand in hand with an increase of cell division rate in the proliferative subset of reactive astrocytes. These results bring new insight into the injury-induced plasticity of reactive astrocytes in vivo and how this potential might be unleashed in a pathological environment.

Optic flow induces vestibular self-motion aftereffects

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In this study, we investigate visuo-vestibular cross-modal aftereffects. To this aim, we measured the physical motion needed to cancel self-motion aftereffect elicited by visual-only adaptation inducing vection. Experiments were conducted using a motion platform, equipped with a 3D monitor. Subjects performed a discrimination task to assess the stimulus value corresponding to zero motion. On each trial a forward or backward movement was presented and subjects indicated the direction they moved. Next stimulus magnitude to be presented was selected based on an efficient adaptive procedure (PSI method), which chooses the stimulus that minimizes the uncertainty associated with the estimate of the zero-motion point. The no-adapter condition was run first and provided a baseline measurement of inherent bias of each subject. In the subsequent forward- and backward-adapter conditions, we present a visual adapter before each movement consisting of 15s 3D optic flow simulating linear translation. Subjects completed each condition in a separate block. In both adapting conditions a significant shift of the zero motion point was observed in the same direction as the visually simulated movement. In other words, consistent with aftereffect patterns, movement in the direction of the adapter was needed to cancel the illusory movement

in the direction opposite the adapter. Thus, we objectively quantify the magnitude of the cross-modal self-motion aftereffect for the first time. Because this effect transfers from visual to vestibular modality we hypothesize that it reveals important properties of multimodal self-motion mechanisms in the brain.

Hippocampal and cortical activations responses to indistinct visual motion and noise stimuli

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Top-down and bottom-up processing streams act in parallel to control the flow of information among brain regions at different hierarchical levels. The predictability of the current sensory stimulus is an important factor that determines the optimal combination of top-down and bottom-up effects. Regions of the brain, like the hippocampus, which are sensitive to measures of irregularity such as entropy (Strange et al., 2005) and mutual information (Harrison et al., 2006) or to the representation of statistical regularities (Schiffer et al., 2012) may influence the relative contribution of sensory input and recurrent feedback for processing visual stimuli.

Recently, we showed higher BOLD activity in hippocampus and early visual cortex when subjects watched noise-like phase scrambled videos compared to watching a movement through a virtual tunnel, although the same spatiotemporal amplitude spectrum was the same (Fraedrich et al., 2010, 2012). There are two possible reasons for hippocampal involvement in processing these indistinct visual stimuli. It is possible

that cortico-hippocampal networks could be recruited for memory retrieval when visual stimuli have systematic structure but still do not reveal a clear meaning. Alternatively, hippocampus activity might be completely independent of meaning but related to the level of uncertainty of the stimulus.

Predictive coding allows updating the model of internal representations if there is a prediction error. Otherwise, it suppresses the redundant flow of information in a feedforward manner at each level of cortical hierarchy. Hippocampus might also encapsulate these predictive coding elements for predicting lower BOLD activity for expected input compared to unpredictable input even (if not only) at low level characteristics of visual input. Here, we test these alternatives by including a white noise stimulus with very high entropy (high spatial and temporal uncertainty), which is completely meaningless. We found significantly higher activities in early visual cortex and hippocampus for random noise stimuli when compared to the other two types of stimuli. This finding suggests that hippocampus is involved in the processing of visual stimuli with a high level of uncertainty even if they are completely meaningless.

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Mindful attention to breath regulates emotions via increased prefrontal cortex-amygdala connectivity

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Introduction:

Mindfulness refers to paying attention to experiences in the present moment with an attitude of acceptance, and can be considered a self-regulatory process. Studies indicate improvements in psychiatric symptoms and general well-being following mindfulness training. A basic mindfulness technique is focused attention to breath (ATB), which has been shown to yield beneficial regulatory effects on negative emotions. Based on data from mindfulness and emotion regulation research, we tested whether the integration of dorso-medial prefrontal cortex (dmPFC) and amygdala present the neural correlate of regulation by ATB.

Methods:

After two weeks of training ATB, 26 health controls were stimulated with aversive pictures during both ATB and passive viewing while undergoing fMRI to investigate whole brain activations and amygdala connectivity using psycho-physiological interaction.

Results:

The ATB compared to passive viewing contrast revealed down-regulated amygdala activation, which was also correlated with regulation success (i.e., subjective valence ratings). The same contrast showed increased right amygdala–left dmPFC connectivity, which was significantly correlated with the participants' ability to focus on the present during training sessions. Activation and connectivity clusters overlapped in the rostral portions of the left supplementary motor area (SMA).

Discussion:

Results relate well to existing literature of emotion regulation and meditation research. Implications for treatment of psychiatric disorders are discussed.

Conclusion:

The data provide evidence for a potential neural pathway of emotion regulation by mindfulness training.

The embryonic development of the nervous system of the grasshopper antenna: axogenesis of the pioneer neurons

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Pioneer neurons are the cells whose axons first establish a pathway which later-developing neurons follow. Pioneer neurons have been found in the developing nervous systems of many different animals and use similar navigational mechanisms. At about one-third embryogenesis, the first pair of pioneer neurons of the grasshopper antenna delaminate from the epithelium at the tip of the antenna. Another pair of tip pioneers appears the same way slightly later. As the axons of the tip pioneers make their way towards the brain, they encounter base pioneers, which originate from the mesectoderm, as revealed by Mes3 immunolabeling. The pioneer neurons of the antenna establish two nerve tracts- one dorsal and one ventral- that lead from the tip of the antenna to the brain; later in development, the axons of sensory neurons fasciculate with these nerve tracts and follow them to their targets in the antennal lobe. The axons of a pair of tip pioneers need to encounter a base pioneer before they can find their way to the brain; this involves the cell-surface glycoprotein Lazarillo, which is expressed by both tip pioneers and base pioneers. In a Lazarillo immunoblocking

experiment, the growth cone of the tip pioneers failed to recognize the base pioneer and stalled in the middle of the antenna instead of continuing to the brain.

Pre- and postsynaptic refinements in the medial superior olive (MSO) during late postnatal development

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Binaural coincidence detector neurons of the MSO process sound localization cues with microsecond precision by integrating excitatory and inhibitory inputs. The inhibitory input to these neurons has been shown to refine around hearing onset in an activity-dependent manner, and is accompanied by severe developmental changes in the cell's biophysical properties. To further understand the refinement mechanism, we investigated the developmental regulation of calcium entry in MSO neurons. Calcium is an important second messenger, potentially associated with developmental alterations. Whole-cell recordings were carried out in acute slices from Mongolian gerbils around hearing onset at postnatal day (P) 10-15 and at mature stages (P60) to image calcium transients evoked by synaptic and action potential (AP) stimulations. Even after hearing onset, a strong calcium influx could be evoked by both APs and EPSCs. However, from P13 onwards the AP-evoked calcium influx decreased rapidly to undetectable levels at P60, as a consequence of reduced AP amplitude and a

downregulation predominantly of a T-type calcium current. Moreover, the NMDAR component of the EPSC declined drastically from P13 onwards. Additionally, the quantal content of the EPSC increased in agreement with morphological changes indicated by calretinin stained input fibres. At mature stages, a significant dendritic calcium transient was still driven locally by the AMPAR component. Our data suggest that calcium entry shifts from its pre- and postsynaptic activity dependence to predominantly presynaptic activity dependence. However, the presence of AP- and EPSC-evoked calcium signals just after hearing onset suggests the persistence of refinements after hearing onset.

Expression profile of voltage gated K^+ channels in the Medial Superior Olive

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Neurons in the Medial Superior Olive (MSO) code for the localization of azimuthal sound sources, by comparing the different arrival times of the sound at the two ears. This time difference, known as Interaural Time Difference (ITD), is in the order of a sub millisecond time scale. Such short integration times require specialized cellular adaptations. One adaptation is to decrease the membrane time constant by increasing the resting conductance e.g. the resting input resistance. The low input resistance of these neurons depends on the activation of hyperpolarization-activated cation channels (I_h channels) (Baumann et al., 2013, Khurana et al., 2012) and low-voltage activated potassium channels (Scott et al., 2005 ; Mathews et al., 2012). In the MSO mainly the low-voltage activated potassium channel Kv1.1 has been shown to be present (Scott et al., 2005; Tong et al., 2010, Mathews et al., 2012). This channel appears to be expressed predominantly at the soma and proximal dendrites of mature MSO neurons. However, other potassium channel subtypes cannot be excluded and it has been indicated from dendritic recordings that the local excitatory postsynaptic potential can be as large as 80 mV (Mathews et al., 2012) enabling the activation of high-voltage

activated potassium currents. Such high-voltage activated potassium currents could counterbalance local excitation. This might be of special importance at dendritic locations as the dendrites of mature MSO neurons receive less inhibitory inputs (Couchman et al., 2012).

The aim of this study was to achieve an overall expression profile of the low- and high-voltage activated K^+ channels in the mature MSO of Mongolian gerbils (*Meriones unguiculatus*). Using immu-nohistochemical stainings and semi-quantitative distribution analysis we are able to show that both low- and high voltage activated K^+ channels are present in MSO neurons and that they show a different spatial profile along the soma-dendrite extent.

Diffusion Tensor Imaging and Tractography identify structural changes in cryptogenic focal epilepsy

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Aim:

To investigate the contribution of Diffusion Tensor Imaging (DTI) and Diffusion Tensor Tractography (DTT) in identifying abnormalities in MRI negative patients with cryptogenic focal epilepsies.

Methods:

18 patients with cryptogenic focal epilepsy were investigated. DTI data was acquired on a GE Signa HDx 3T Scanner, using an acquisition scheme with 64 diffusion weighted directions, a b-value of 1000m/s², 2.4 mm slice thickness and 2 mm in-plane resolution. Fractional anisotropy (FA) maps were investigated for focal changes and asymmetries. Streamline DTT of the whole brain was used as an exploratory method in the absence of a structural lesion and the number of reconstructed streamlines in homologous anatomical areas of the left and right hemisphere was compared.

Asymmetries of more than 10% for FA maps and less than 20% for the streamline count were rated as a significant finding.

Results:

In about 75% of patients, visual inspection identified asymmetries in the number of reconstructed streamlines. In 80% of all patients, the changes obtained through quantification were consistent with the clinically suspected seizure onset zone, based on video-EEG-monitoring and nuclear medicine data. However, in two patients DTT indicated more widespread, hemispheric changes, beyond the seizure onset zone. FA maps show asymmetries beyond 10% in only one patient. In two patients, the seizure onset zone was confirmed in the area of DTT abnormalities by intracranial electrodes, the other patients are still awaiting invasive evaluation, including the one with discrepant DTI findings.

Conclusions:

These preliminary data show the potential role of DTI and DTT, as a complementary lateralizing and localizing imaging modality in the presurgical evaluation of cryptogenic epilepsy patients. We hypothesize that the observed changes reflect migration disorders, where heterotopic neurons disrupt the microstructural order of white matter underlying the seizure onset zone. Further interpretation of theses findings requires follow up studies with intracranial electrodes and a correlation with histopathology. DTT appears to be more sensitive than FA maps, and this method may be less sensitive in patients with small-circumscribed focal pathologies compared to patients with a more widespread pathology.

Characterizing gerbil hippocampal activity in virtual reality

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Neuronal activity in the hippocampus and its relation to the encoding of space has mostly been studied in freely behaving rats and mice. Here, we report on data recorded in CA1 and CA3 hippocampal subfields of Mongolian gerbils in virtual reality (VR). Using a VR, we can study the impact of visual cues on place cells independent of self-motion cues. In both, real and virtual environments, we find hippocampal place cells that encode specific locations by their place fields. When the animal moves through such a place field, place cell spikes precess relative to hippocampal theta oscillations (phase precession). As in rats and mice, the local field potential (LFP) of Mongolian Gerbils has high power in the theta range (4-12 Hz). In virtual reality however we find that theta frequency reduces in comparison to theta recorded in real environments. During periods of immobility or slow wave sleep (SWS), place cells are taking part in population bursts that are temporally correlated to sharp wave-ripple

(SWR) complexes. Our results show that firing patterns of hippocampal place cells in VR are largely similar to those in real environments.

Expect to be distracted: Prediction of salient distractor by action and cue attenuates its interference

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Action and perception are known to be tightly linked. It has been found that predicted sensory consequences of actions are perceived with an attenuated intensity. Sensory attenuation has been demonstrated in the tactile and auditory domains, but the evidence is sparse in the visual domain. This predictive attenuation seems to be in conflict with attentional mechanisms which can enhance sensory processing at a location where a target has been predicted to appear. We aimed to investigate the consequences of making a salient task-irrelevant distracting item predictable in an attentionally demanding task in which it generally captures attention. Our aim was thus to examine the interaction between prediction and a stimulus-driven attention. First, we wanted to see whether the usual interference caused by the distractor will be attenuated or enhanced when its presence and location is reliably predictable. Several studies going in this direction have found conflicting results. Second, we wanted to test whether there is a difference between making the distractor predictable by a previously associated action and by an endogenous cue. While some theories predict

an effect of action on top of the cue, the influential predictive coding accounts predict no such difference, given the outcome can be predicted with the same precision in both cases. Our results show a clear attenuation of the distractor interference when it is made predictable. However, prediction by action had the same magnitude and spatial pattern of influence as prediction by cue, even though our study was reasonably powered to find a difference here based on previous literature. In conclusion, our findings are consistent with the predictive coding accounts of attention and sensory attenuation suggesting the existence of a more general predictive process, even though the possibility of two distinct processes cannot be excluded. Our results also demonstrate an effect in opposition to the so-called "attentional white bear" phenomenon showing that knowledge of a distracting item needs not have an adverse effect on perception but can in fact improve it to some degree.

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Spike generation and integration of synaptic currents in a model of CA1 pyramidal cells during sharp-wave ripples

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Pyramidal cells in the hippocampus are found to be active at certain locations in space, when a rodent is moving through an environment. Having the spiking activity of several of these place cells allows to reconstruct the trajectory of the animal. During awake immobility and slow-wave sleep a replay of these sequences on a faster timescale can be observed. The underlying local field potential is characterized by high-frequency oscillations (~150-200 Hz) with large voltage deflections, known as sharp-wave ripples (SPW-Rs). These sharp-wave ripples are thought to play a major role in memory consolidation and emerge from activity bursts in the hippocampal area CA3. The cellular mechanisms underlying replay during sharp waves are not well understood. To investigate these properties we implemented a biophysical multi-compartment model of a CA1 pyramidal neuron. The model can generate action potentials when realistic synaptic currents are used as inputs.

Optogenetic dissection of tectally controlled orientation behavior in zebrafish larvae

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In order to generate target-oriented behavior, sensory information needs to be integrated and converted into a pattern of activity in downstream premotor areas. While it is known that the optic tectum performs this 'sensorimotor transformation', its cellular and synaptic underpinnings remain unclear. Using two experimental strategies, we test the role of the optic tectum in orienting responses (e.g. tail and eye movements) and functionally dissect the underlying neuronal circuitry.

To investigate the tecto-reticular connectivity of different tectal zones, the tectum was optogenetically mapped for different behaviors. Experiments were conducted at 5 dpf, when zebrafish larvae start to show consistent visual behavior. Fish were stimulated using an optic fiber while behavior was recorded using a high-speed camera. Observed tail movements can be divided into different behaviors, such as: orientation, approach and escape. Using fish coexpressing *ChR2* (*channelrhodopsin-2*) and *paGFP* (*photoactivateable GFP* - using UV-light), the stimulated tectal area can be investigated. First results indicate that different tectal stimulation sites induce different behaviors. Control fish were treated in the same way, but solely expressed the afterwards activated *paGFP*.

In order to determine the neuronal substrate of the tectal line governing the different behaviors, we started to use a single cell mosaic labeling technique. Taking advantage of a highly variegated GFP fish line (*BGUG*), single neurons can be labeled in the tectum. This allows us to classify e.g. the ipsilateral and contralateral tract at single cellular resolution or as 'genetic Golgi'. Screening for neurons localized in the stimulation areas in the different tectal zones will reveal distributions of neuron types and targets (e.g. reticular formation) of tectal projection neurons.

Probing interval timing in rodents with virtual reality

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The ability to estimate time intervals in the range of seconds to minutes is critical to many of our cognitive abilities. However, the underlying neural mechanisms are still not well understood. To tackle this problem, we propose implementing timing tasks in virtual reality (VR) as an extension of classical approaches. VR setups for rodents recently became popular, since with them advanced neurophysiological recording techniques can be used in the behaving animal.

We designed two different tasks, based on well-known interval timing tasks, to probe time perception in rodents in VR. Our tasks require estimating temporal intervals while running along a virtual hallway. Using VR we can ensure that the animals indeed perform time estimation. In VR the test environment can be designed without prominent spatial cues thereby preventing alternative solution strategies. In addition, movement speed and optical flow can be de-correlated, such that the animals cannot learn a mapping between stimulus duration and running distance. The first task is a modified ready-set-go task in which the animals estimate the duration of a visual

stimulus and reproduce it by running. This behavioral readout allows for responses on a continuous scale. In addition, specific intervals do not need to be trained beforehand. The second task is a time bisection task. Here, the animals are asked to estimate the time they run down the hallway until the projection switches to a Y-shaped maze. They then need to choose either the left or the right arm of the Y-maze to report if the interval was perceived as long or short, compared to previously trained reference intervals.

We successfully used the above tasks in experiments with Mongolian gerbils and present data from experiments in which we tested timing of durations between 2 and 13 seconds. The results are consistent with reports from previous studies and hence demonstrate the applicability of our approach to probe interval timing in rodents.

The Impact of Body Orientation on Human Heading Perception

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Self-motion information can be estimated from visual optic flow and vestibular signals, but often with systematic biases for non-cardinal directions. These biases are in part due to the influence of prior knowledge or expectations on the type of self-motion that occurs. One prior expectation may be related to the position of the body with respect to the world. When we move through the world, we typically do so in an upright position, for instance, when walking or driving a car. Self-motion cues are less common while lying down. It is therefore not clear how visual and vestibular heading estimation is affected by the change in body orientation.

In this study, we tested the effect of body orientation on heading estimation accuracy for a) the visual system using 3D optic flow stimuli and b) the vestibular system using whole body movements generated on a motion platform. Twenty-four different heading directions in the body-horizontal and body-vertical plane were presented once in a supine and once in an upright body orientation. Eleven subjects estimated their perceived direction of self-motion. For both visual and the vestibular stimulation, heading estimation accuracy showed systematic biases that varied with the presented

heading direction. Only during vestibular stimulation were considerable effects of body orientation found.

These findings suggest that although the vestibular system is affected by the change of body orientation, there is no apparent impact on the visual system. This may be expected as the otolith organs of the vestibular system respond to linear accelerations as well as gravity. These results are also relevant for neuroimaging studies investigating human visual self-motion perception. MRI requires a supine position, and it was previously assumed that our knowledge of visual self-motion estimation from behavioral studies also applies to a supine body position. Here we support the transferability of findings from upright behavioral studies to supine fMRI studies of heading estimation.

Contextual interactions in a non-uniform population code: An application to human color vision

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The perceived color of an object depends not only on the spectral composition of the light reflected from its surface, but also on the visual context such as illumination and background color. Such contextual interactions are thought to underlie perceptual phenomena like color constancy. A possible neuronal basis may be lateral interactions which manifest in contextual influence on the tuning of color-selective neurons in the visual cortex (Wachtler et al., 2003).

Here we present a model of cortical color processing that predicts color shifts induced by chromatic backgrounds as observed in psychophysical studies. The model assumes that stimulus hue is encoded by a population of neurons with Gaussian tuning curves and preferences distributed in color space, corresponding to the finding of distributed color preferences in primary visual cortex (Lennie et al 1990). Lateral inhibitory interactions between neurons sharing the same color preferences are modeled by a Difference-of-Gaussian interaction kernel. No interactions between color channels are

assumed. Due to the contextual modulation the readout of the population response showed systematic shifts in the encoded stimulus hue when stimuli were presented on colored backgrounds. The induced shifts depended on the distance between stimulus and background hues in colorspace, but were always directed away from the hue of the background. The specific shapes of the resulting induction effects strongly depended on the configuration of the population code, like the density distribution and widths of the tuning curves. Specifically, anisotropic distribution of tuning curves resulted in dependencies of the induction strength and distribution on the location in color space, in line with effects observed in psychophysical studies. The results indicate that important computations in color vision that lead to perceptual hue shifts can be realized using simple neural mechanisms when color is represented by a distributed code.

Unraveling mechanisms of photoreceptor degeneration in Achromatopsia

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Vision in mammals is controlled by the second messenger cyclic guanosine 3′-5′-monophosphate (cGMP). In the dark cGMP maintains the cyclic nucleotide-gated (CNG) cation channels in the open state. Mutations in the CNGA3 subunit of the CNG channel result in a slow progressive cone degeneration and cell death. This severe retinal disease is known as Achromatopsia.

The loss of the CNG-channel results in a low intracellular Calcium-level, leading to an activation of the retina-specific guanylyl cyclases E (GCs). The mouse model of Achromatopsia shows a progressive cone degeneration and an accumulation of cGMP. A known target of cGMP is the cGMP dependent kinase I (cGKI), expressed in the retina. Overexpression of a constitutive active form of cGKI leads to fast degeneration of the outer nuclear layer. A microarray additionally identified differentially expressed genes in the CNGA3 ko mouse. Specific gene groups and pathways associated to the disregulated gene transcripts could be identified.

Watching the assembly of a toy model entrains the cortical activity between the observer and the constructor

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Humans as social beings constantly have to make sense of the movements and actions of others. The cortical action-observation system includes human counterparts to mirror neuron areas found in non-human primates (Rizzolatti et al 2004). However, most previous fMRI studies have used simplified approaches not assessing the direct cortical relation between action and observation.

We want to investigate the cortical activity of realistic and natural actions, and the observations thereof. Therefore, we chose the construction of a children's toy model as the subject of this fMRI study. We grouped participants in pairs, with one participant building the toy, the other one observing the construction process.

We analyzed the data applying the inter-subject correlation method (Hasson et al 2004). By using this method we can compare two subjects' BOLD-signals in

corresponding voxels in order to identify similar time courses during action and observation. High similarities are expected to occur in brain areas with postulated mirror properties (Molenberghs et al 2012).

We observe significant correlations ($p<0.05$, TFCE, FWE corr.) in visual areas, superior parietal lobule, postcentral gyrus and precentral gyrus. Similarity in visual activations is to be expected as both participants are receiving the same visual stimuli. However, the other clusters indicate significant similarity in areas associated with mirror properties. This finding is consistent with the postulated existence of mirror neurons in these areas.

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Transcriptome analysis of the adult neural stem cell progeny reveals chromatin remodeling as a prominent process in the adult neurogenesis

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Neural stem cells in the adult mammalian brain serve as a basis for adult neurogenesis due to their capacity to self-renew and generate new neurons in restricted brain areas, called neurogenic niches. Although the stem cell identity and neurogenic lineage have been well defined, the genetic program for adult neurogenesis taking place in these cells is poorly understood. Therefore, transcriptome analysis of neurogenic cell populations is required to identify genes and biological processes involved in generation of new neurons. While our lab has previously determined the genome-wide expression pattern of neural stem cells (Beckervordersandforth et al., 2010), the transcriptome of their progeny, the neuroblasts or oligodendrocyte progenitor cells (OPCs), has not yet been characterized. Therefore, we prospectively isolated the neuroblasts, OPCs and oligodendrocytes utilizing surface antigens and fluorescence

activated cell sorting method (FACS). Using Affymetrix Gene 2.0 ST arrays we determined the transcriptional profile of these three populations. In further analysis we characterized the genes enriched specifically in different populations and revealed biological processes and pathways in which are these genes involved. Our analysis identified the neuronal differentiation and chromatin remodeling, as prominent biological processes enriched in progeny of neural stem cells. This evidence indicates that chromatin-based transcriptional regulation is a key epigenetic mechanism for the life-long function of adult NSCs and their progeny. However, chromatin-remodeling factors that regulate neurogenesis in the adult mammalian brain remain to be explored. Therefore we aim to further characterize the role of chromatin remodeling in the adult neurogenesis, by performing expression analysis and functional analysis of selected candidates.

High mobility group B proteins (HMGB) is the family of chromatin-remodeling factors, which are known of their capacity to induce the structural changes in the chromatin fiber. The high expression of HMGB2 protein specifically in the progeny of the neural stem cell could suggest on its possible involvement in process of generating functional neurons from adult neural precursors. Towards the understanding of its possible role, we performed gain and loss of function experiments in vitro and in vivo. In vitro experiments revealed that HMGB2 overexpression promotes the proliferation of neurospheres. In vivo, higher levels of this protein led to slightly increased proportion of the neuroblasts in the subependymal zone suggesting the increase in the neurogenesis. With the further functional and molecular analysis we would like to better characterize HMG proteins and shed some light on possible contributions of HMGB2 and epigenetic mechanism chromatin remodeling to the adult neurogenesis.

Translating rodent limbic theta to humans: a simultaneous EEG/fMRI study of fear conditioning and extinction

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Adaptive fear and safety learning are crucial for well-being and psychological health. Some psychological disorders like post-traumatic stress disorder (PTSD) or anxiety disorders show altered and maladaptive fear learning patterns and impaired safety learning. These learning mechanisms can be closely modelled with fear conditioning and extinction tasks. During fear conditioning a neutral stimulus is continuously presented together with an aversive event. It thereby becomes a conditioned stimulus which provokes the anticipation of the negative event. During extinction, the conditioned stimulus is presented, but without the anticipated negative event, so that safety learning occurs and the stimulus can be perceived as neutral again.

Numerous studies using functional magnetic resonance imaging (fMRI) have shown, that such fear conditioning and extinction processes in the human brain involve an interplay between limbic and paralimbic brain areas like amygdala, insula, anterior cingulate cortex (ACC), hippocampus and medial prefrontal cortex (mPFC). Yet still it is unclear, through which oscillatory mechanisms these brain regions interact in

humans and which alterations are correlated with maladaptive fear and safety learning. Experiments including intracranial electroencephalographic measurements (EEG) in rodents have shown that the extent of theta synchronisation between amygdala and other regions relevant for fear learning (dACC, mPFC, hippocampus) is correlated with the fear reaction evoked by a fear conditioned stimulus and with fear memory recall. This theta synchronisation in the frequency range of 4-8 Hz seems to be a relevant marker for both the acquisition and expression of fear and safety in rodents. However limbic theta in rodents may not completely correspond to human theta oscillations: in REM sleep for instance, a strong synchronisation of limbic areas in the theta rhythm occurs in rodents, whereas initial evidence suggests that intracranial oscillations in the human hippocampus during REM sleep are most pronounced in the 1.5-3 Hz range. Furthermore, the imprint of hippocampal theta on surface EEG is not fully understood yet.

Our study therefore aims to now translate these findings to the human brain and to complement the knowledge from fMRI with information about neural oscillations with surface EEG. Initial analyses have already revealed that the coupling of left amygdala and dorsal ACC during fear conditioning seems to be mediated by the power of theta oscillations also in the human brain, but unclear is whether this represents anticipatory fear, unconditioned stimulus processing or conflict/error signalling. The current study investigates neural oscillations measured with scalp EEG that are associated with the interaction of limbic and prefrontal regions in the human brain during fear learning and extinction processes. It also addresses the question whether it is possible to obtain an appropriate marker from EEG data which reflects the functioning of fear and safety learning processes.

Simultaneous EEG, fMRI and skin conductance response (SCR) measurements will be acquired during a fear conditioning task with a subsequent extinction session. We will examine the responses of young, healthy participants, who will be confronted with coloured geometrical stimuli, partly coupled with mild electrical shocks. Data processing will involve EEG frequency analysis, fMRI activity and connectivity analysis as well as integration of EEG and fMRI data in regions of interest like bilateral amygdala, mPFC and dACC. Results and their implications will be discussed.

Sensorimotor feedback maintains auditory objects formation in zebra finches (Taeniopygia guttata)

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Sound cannot be known as an object independently without sensory experience (Griffiths & Warren, 2004). The brain must have a role in auditory object formation from acoustic events. Both birdsong and human language are learned vocalization and auditory objects. They are complex, diverse and rarely heard in isolation. Birdsong or speech is often heard in a competing acoustic environment. In an international cocktail party for instance, people are able to identify those who speak the same languages from background noise easier than those who speak other languages. It suggests that there must be neural mechanisms for a listener to maintain the sensitivity of his own language.

Patients with damage to the Broca's area suffered from aphasia, but also had difficulty in speech comprehension, which implies that sensorimotor feedback may influence speech perception. In zebra finch, the sensorimotor nucleus HVC (higher vocal center) corresponds functionally to Broca's area. Both HVC and Broca's area were mostly studied in sensory-motor interaction for speech production and learning, whereas

sensorimotor feedback in speech perception is less known. The aim of this study is to investigate the influence of HVC on auditory object formation.

Reprogramming of glia cells into mature neurons after injury in vivo

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Neuronal death is a common phenomenon occurring following acute injury to the central nervous system (CNS). Dead neurons are not replaced after stroke causing permanent neurological defects. Glial cells (astrocytes-OPC-microglia) proliferate and become hypertrophic to occupy the injured areas after damage performing the wound reaction and scar formation (Robel et al. 2011; Dimou and Götz, 2014). The ideal approach for neuronal repair is to convert the scar-forming glial cells into neurons. Pioneering in vivo approach has already demonstrated the possibility to convert resident glia cells into neurons (Buffo et al. 2005; Kronenberg et al., 2011) however the process is rather inefficient.

The challenge of the next years will be convert resident glial cells in the brain into specific subtypes of neurons after injury. The aim of this project is combine different neurogenic transcription factors to convert glial cells in different neuronal subtypes as a strategy for neuronal repair after injury. Preliminary observations show that with our strategy we can target mainly astrocytes and OPC cells and different combinations of

transcription factors reveal some potential candidates for reprogramming after CNS injury.

Genetic predisposition interacts with early-life stress in a mouse model of affective disorders

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Exposure to severe stress in early life is a potent risk factor for affective disorders. An individual's genetic background plays an important role in mediating the effects of stress towards increased vulnerability or resilience. However, the pathways by which this interaction occurs remain poorly understood. In a set of experiments, we attempted to model the clinical situation of a genetic vulnerability interacting with a stressful environment during a critical period of development to analyze the resulting molecular, neuroendocrine and behavioral changes.

We used a genetic mouse model for altered stress reactivity (SR mouse model) consisting of three independent CD1-derived mouse lines, bred for high (HR), intermediate (IR) or low (LR) HPA axis reactivity in response to a stressor.

From postnatal day 2-9 a group of mice from each of the three breeding lines was exposed to a chronic early-life stress paradigm (limited nesting & bedding material), while a control group of each line was raised in standard housing conditions.

Bodyweight and plasma corticosterone concentration were assessed at several time points throughout the experiment as indicators of stress and delayed development. At twelve weeks of age, the adult mice were tested to assess their emotional behaviour, stress-coping, cognition and neuroendocrine function, as well as molecular changes in gene expression.

The results confirmed that the early-life stress manipulation was effective in all three lines, as evidenced by a reduced weight gain in stress-condition pups compared to controls. In addition, we found a significant interaction between genetic background and stressful environment in the pups' basal corticosterone level and relative adrenal weight and in the animals' stress-coping behaviour and HPA axis reactivity in adulthood. Mice with a genetic predisposition for high stress reactivity (HR) were more affected by the early-life stress exposure than animals from the less reactive mouse lines (IR and LR).

Taken together, we were able to demonstrate a clinically relevant gene-environment interaction of early-life stress exposure and genetic vulnerability. The presented model can be a powerful tool to gain further insight into the role of early life adversity in affective disorders and to investigate the underlying molecular processes.

Brain Connectome in Major Depression and Preterm Born Individuals at Risk for Depression

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In human brain information is continuously processed and transported among structurally and functionally connected regions. Recently the MRI-based macroscopic brain connectome is used to explore brain organization in the multidisciplinary research of neuroscience and in-vivo brain mapping, which conceptualizes the whole set of brain regions and their interconnections as a complex system (showing such as small-world property, global efficiency, and network hub). In clinical neuroscience, it is crucial to understand aberrant organizational patterns in disordered brain and at-risk state.

Here, we investigate whether brain connectome methods can uncover altered functional organization in major depressive disorder (MDD) and preterm born adults at risk for depression. MDD is one of the most frequent mental disorders and 50% of MDD have recurrent multiple depressive episodes in the disorder course. Preterm

birth leads to higher neonatal risk, adverse neurodevelopmental outcomes, and significant risk for depression in adulthood. In our studies, MDD group, preterm group, and their control groups were recruited separately. Resting-state fMRI was acquired for spontaneous brain activity. Brain connectome, mathematically depicted by the graph, was constructed by Harvard-Oxford-atlas-based parcellation (i.e. node) and low-frequency synchronized activities (i.e. edge). Brain's topological organization was assessed by graph-theoretical network analysis. Permutation testing was utilized for group comparisons while detected alterations were further associated with clinical and/or behavioral data.

Current results of affected brain connectome shed new insight to neural correlates of major depression and early life risk factor such as preterm birth. We conclude that (i) human brain embeds system-level complex organization and (ii) both major depression and risk factor of preterm birth link with disrupted brain organization. Data suggest brain connectome as a potentially common intermediate phenotype for brain diseases.

A model for non-monotonic intensity coding

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Peripheral neurons of most sensory systems increase their response with increasing stimulus intensity. Behavioural responses, however, can be specific to some intermediate intensity level whose particular value might be innate or associatively learned. Learning such a preference requires an adjustable transformation from a monotonic stimulus representation at the sensory periphery to a non-monotonic representation for the motor command. How do neural systems accomplish this task? We tackle this general question focusing on odour intensity learning in the fruit fly, whose first- and second-order olfactory neurons show monotonic stimulus-response curves. Nevertheless, flies form associative memories specific to particular trained odour intensities. Thus, downstream of the first two olfactory processing layers, odour intensity must be re-coded to enable intensity-specific associative learning. We present a circuit motif that implements the required transformation by combining excitation, inhibition, and, as decisive third element, homeostatic plasticity. Key

features of the circuit are consistent with the known architecture and physiology of the fly olfactory system. The simplicity of the circuit and the robustness of its function under parameter changes suggest that this type of network is also relevant for other neural systems and make it well suited for implementation in neuromorphic hardware.

Altered intrinsic connectivity indicates compensation of attention deficits in preterm born adults

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Although pronounced and lasting deficits in selective attention have been observed for preterm born individuals it is unknown which specific attentional sub-mechanisms are affected and how they relate to brain circuits.

We used the computationally specified 'Theory of Visual Attention' together with whole- and partial-report paradigms to compare attention sub-mechanisms of pre- and fullterm born adults. Resting-state fMRI was used to evaluate both between-group differences and inter-individual variance in changed functional connectivity of intrinsic networks relevant for visual attention.

In preterm born adults, we found specific impairments of visual short-term memory storage capacity (vSTM) while other sub-mechanisms such as processing speed or attentional weighting were unchanged. Furthermore, changed functional connectivity

was found in thalamic, unimodal visual and supramodal attention-related networks. Among preterm born adults, the individual pattern of changed connectivity in occipital and parietal cortices was systematically associated with vSTM in a way that the more distinct connectivity differences the better preterm adults' storage capacity.

These findings provide first evidence for selectively changed attention mechanisms in preterm born adults and their relation to altered intrinsic brain networks. In particular, data suggest that cortical changes in intrinsic functional connectivity may compensate adverse developmental consequences of prematurity on visual short-term storage capacity.

Modeling the Dendritic Spine Response. A First-Principles Approach

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Dendritic spines, the postsynaptic structures involved in excitatory chemical transmission, display highly diverse morphologies. Variations in spine conformation presumably underlie the effective strength of the synapse. In the most extreme case, cable theory predicts that the spine head electrically decouples from the parent dendrite. Yet spine neck resistance is only indirectly measurable, which has led to considerable debate as to the true value of the resistance. A crucial question is whether the macroscopic biophysics underlying cable theory even applies: the small spatial extent of spines, accompanied by numerous ultrastructural elements that crowd the interior of the spine, could potentially lead to nonlinear current-voltage relationships.

Here we present a framework that includes all the necessary morphometrical and physiological details for precisely estimating the current conduction characteristics within these nano-scale domains. Amongst these are: the precise number, kinetics and

position of postsynaptic receptors, fully 3D geomtery of the spine accompanied by cytoarchitectural ultrastructure, all of which sets the foundation for accurate biophysical modeling.

Optogenetic manipulation of the lateral septum in mice selectively bred for high anxiety-related behaviour

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Anxiety disorders affect 13.6% of Europe adult population and yet remain still inadequately treated. The lateral septum (LS) is crucially involved in emotional processes and stress responses related to anxiety. However, previous experiments were limited to chemical/electrical stimulation, which lack cell or projection specificity. A possible solution to overcome these issues is to target specific projections to the LS and try to correlate their function to behaviour.

In this project we assessed the involvement of the afferent projections to the LS originating from the ventral hippocampus (vHPC) in the expression of anxiety-related behaviour of mice selectively bred for high levels of anxiety-related behaviour (HAB). We achieved projection-specific inactivation of LS by means of optogenetic techniques and we assessed anxiety-related behaviour in the elevated plus maze (EPM) and the open field (OF) tests. Altogether, this approach allowed high control, both in time and space, of the activity of the LS during the selected behavioural paradigms.

We found that optogenetic inactivation of LS cells labelled through the projections coming from the CA1-CA3 region of the vHPC does not have an effect on the anxiety traits which were evaluated with the employed behavioural testing procedures. We believe that targeting other subpopulations using the same experimental procedure could nonetheless reveal new insights about the lateral septum circuitry and clarify its role in the pathophysiology of anxiety disorders.

Social perception is modulated by expectations regarding others' action goals

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Social interactions require the ability to predict and understand others' behavior and its underlying intentions. In order to infer intentions and action goals, humans pick up various social signals, such as the others' gestures or gaze direction, providing information about their focus of attention or intended action steps. The present study examined the mechanisms of gaze following in the context of participants' expectations about successive action steps of an observed actor, by embedding a gaze-cueing manipulation within an action scenario depicted in a sequence of naturalistic photographs. Gaze-induced orienting of attention (gaze following) was analyzed with respect to whether the gazed-at object was congruent or incongruent with the overarching action goal. In Experiment 1, participants followed the gaze of the observed agent, though the gaze-cueing effect was reduced when the actor looked at an action-incongruent object. Experiment 2 examined whether the pattern of effects observed in Experiment 1 was due to covert, rather than overt, attentional orienting, by requiring participants to maintain eye fixation throughout the sequence of critical photographs (corroborated by monitoring eye movements), as well as reinforcing the

encoding of the action goal. The essential result pattern of Experiment 1 was replicated, with the gaze-cueing effect being completely eliminated when the observed agent gazed at an action-incongruent object. These findings show that covert gaze following can be modulated by expectancies that humans hold regarding successive steps of the action performed by an observed agent.

Uhrf1, an epigenetic factor, acts as a key regulator of neural stem cell differentiation in vivo

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Understanding the molecular mechanisms of neurogenesis is crucial towards the aim to reactivate this process for repair purposes. In order to identify key regulators of this process, we performed genome-wide expression analysis of adult Neural Stem Cells (aNSCs) isolated by fluorescence-activated cell sorting (Beckervordersandforth et al., Cell Stem Cell 2010). One of the candidates with significantly increased mRNA expression in aNSCs and further increasing in transit-amplifying progenitors (TAPs), is Uhrf1/Np95. Uhrf1 is a multifunctional protein involved in the regulation of epigenetic modifications, such as DNA methylation and histone deacetylation. To understand Uhrf1 function in vivo, we first monitored cell type-specific protein localization. Interestingly, Uhrf1 immunoreactivity was high in NSCs during embryonic neurogenesis, decreasing in TAPs and further during neuronal differentiation. In

contrast, Uhrf1 protein levels are hardly detectable in adult NSCs and high in adult TAPs and neuroblasts. Conditional deletion of Uhrf1 in neural stem cells in the embryonic forebrain showed an increase in ectopic NSCs accompanied by cell death, resulting in a significant reduction in neurons. Genome-wide expression and methylation analysis will be presented in light of the molecular function of Uhrf1. Intriguingly, the phenotype of Uhrf1 deletion differs profoundly between regions, highlighting a highly context dependent function for Uhrf1 in neurogenesis.

Visual experience vs. Decisional confidence: Dissociable measures of consciousness?

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Are subjective reports of visual experience and subjective reports of decisional confidence interchangeable measures of conscious awareness? In a series of psychophysical experiments, we observed that confidence about the accuracy of a discrimination decision is associated with lower psychophysical thresholds and predicts discrimination performance more efficiently than reports of a visual experience. Event-related potentials suggested that the neural events associated with reports of confidence occurred shortly after stimulus presentation, while the strongest correlates of clear visual experiences were not observed until shortly before a discrimination response was made. Moreover, transcranial magnetic stimulation over the occipital cortex increased reports of visual experience, but decreased the level of reported confidence. Finally, while the criteria of decisional confidence were subject to age-related changes, no age affects were observed for reports of visual experience. Taken together, these studies provide converging evidence that visual experience and confidence are distinct measures of consciousness, and a complete study of consciousness requires the assessment of both.

Human Behaviour and Brain Activity in Spatial Exploration

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Spatial exploration is an ecologically relevant behaviour that guides upcoming actions. It is thought to rely on spatial memory, sensorimotor integration as well as forward planning.

To test for these components, we designed a flexible paradigm for spatial exploration in humans, similar to what has been used in rodents. Participants (n=30) navigated freely via joystick in a circular virtual environment (VE) with only one landmark, while their hemodynamic activity was recorded with fMRI. Fifty items were randomly distributed within the VE. Participants could only see items within a certain radius around their current position in the VE, and were given 30 seconds in one condition (SHORT) and 180 seconds in the second (LONG) to collect as many items as possible. In SHORT performance was limited by time and maximum speed, whereas in LONG, spatial memory became increasingly relevant during the task. In a third condition subjects were passively moved through the VE.

Participants showed a variety of exploration strategies that we characterized using path-related measures. These measures suggest that knowledge of one's previous position may not be required for high performance during active exploration. Hemodynamic activity revealed that passive movement through the VE was sufficient to activate a network of brain regions involved in spatial navigation tasks in humans; and that brain areas associated with decision making appear to play an important role in active exploration.

Functional connectivity in obsessive-compulsive disorder in relation to disgusting visual stimuli

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Introduction:

Presentation of disorder specific stimuli may help to unravel the neurobiological basis of obsessive-compulsive disorder (OCD). Respective studies show a disrupted neuronal activation pattern mainly in fronto-striatal and subcortical regions. Little is known about the functional connectivity of these regions during the perception of psychopathological relevant stimuli. This fMRI study aims to investigate the potentially altered connectivity within these networks and its relation to symptom severity and disorder subtype.

Methods:

A sample of 22 OCD patients and a similar sized control group matched for age and gender were presented disgust related pictures from the International Affective Picture System during fMRI scanning. To analyze functional connectivity we applied the

method of Psycho-Physiological Interaction (PPI). Right and left amygdalae were used as seed regions based on a priori univariate analyses. The potential relation between altered connectivity and symptom severity or disgust sensitivity was assessed by correlating the connectivity maps with obsessive-compulsive inventory (OCI-R) scores and disgust sensitivity (FEE) scores.

Results:

We found an increased functional connectivity between left amygdala and fronto-striatal regions in patients compared to healthy controls. Most importantly, there was a bilaterally increased connectivity between the amygdala and the insula in patients compared to healthy controls. Although we observed a significantly increased disgust sensitivity score in the patient group, disgust sensitivity was not significantly correlated with altered neuronal connectivity. There was, however, a positive correlation between washing compulsions severity score and the connectivity between left amygdala and bilateral precuneus.

Conclusions:

Results of this study support our hypothesis that OCD is associated with altered functional connectivity in patients when exposed to disorder relevant stimuli. Further, results indicate an association between severity of washing compulsions and connectivity of the amygdala with a region (i.e., precuneus) critically involved in conscious information processing. This could be explained by the fact that patients focus more intensively on disease relevant stimuli which, in turn, might relate to an increased level of compulsions.

Contextual learning during visual search induces representations of visual context accessible to verbal report

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In visual search, participants can use predictive cues to help guide their attention to the relevant target stimulus. Repeated distractor-layouts can be used as such cues and are learned via repeated exposure to the same search display, this phenomenon has been labeled contextual cueing. Previous research on contextual cueing yields diverging results about the explicitness of long term memory templates: While initial studies claim it is an implicit process, employing recognition tests, other approaches provide evidence that it is at least partly explicit, by increasing test power and using generation tasks, or awareness ratings. We address this issue by using subjective reports about the clarity of the visual stimulus which distinguish between the memory template and the response-defining stimulus. Our findings indicate that spatial contextual learning leads to verbally accessible representations of the visual context but not of the target stimulus. More specifically, the coherence of verbal reports and performance (metacognitive sensitivity) in visual search is strengthened under the condition of search templates stored in long-term memory. We conclude that

contextual cueing yields explicit representations of visual context and that the increase in metacognitive sensitivity is directly linked to the information stored in long-term memory, rather than to the improvement in search behavior.

Early cerebral perfusion deficits after subarachnoid hemorrhage in mice

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In most cases subarachnoid hemorrhage (SAH) is caused by a ruptured aneurysm at the skull base which leads to a bleeding into the subarachnoid space. In patients SAH induces cerebral ischemia early after the insult (Schubert et. al., 2009). Constrictions of superficial cerebral arteries occur early after SAH in humans (Uhl et. al., 2003) as well as in mice (Friedrich et. al., 2011). The impact of microvasospasms on blood flow dynamics in the brain has not been investigated to date. In this study we want to shed light on the evolvement of vascular dysfunction and early cerebral ischemia after SAH. Therefore we visualize the deep cerebral microcirculation after SAH by making use of two photon intravital microscopy. SAH surgery is performed by endovascular Circle of Willis perforation at the skull base. Perfused cerebral vessels are visualized by fluorescent dyes and scanned for various parameters. Regional cerebral blood flow is heavily reduced after SAH, indicating early vascular dysfunction after the bleeding. The arteriolar vessel diameters as well as arteriolar blood flow velocity are significantly reduced after the bleeding. Both parameters induce perfusion deficits at the level of the deep parenchymal microcirculation.

In this in vivo two photon microscopy study we show that cortical ischemia after SAH is caused by microvasospasm of superficial arteries. The reduction of vessel diameter hampers regular blood flow and thereby causes perfusion deficits in the parenchyma. Taken together the evolvement of a pronounced and persistent cerebral ischemia early after SAH can be explained.

Behavioural characterisation of the blowfly gaze stabilisation system

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Gaze stabilisation is an ubiquitous behaviour, and a well-studied control system in the blowfly. Blowfly motion sensitive visual interneurons have long been implicated in this behaviour, and they have recently shown to be sufficient to elicit a head movement resembling an optomotor response in *Drosophila* [1]. It is remains unclear, however, whether and how head movements exhibit an optomotor response, and what the role of motion sensitive visual interneurons is for this behaviour. This work firstly reveals that the blowfly exhibits a head optomotor response and identifies its characteristics. Secondly, it shows that the head optomotor response is dependent on the temporal frequency of the visual stimulation and on the fly's locomotion state. Finally, it shows that visual motion adaptation of the visual system is affecting the head optomotor response. This demonstrates a functional role of visual motion processing neurons of the visual system for the head optomotor response. In summary, this work characterises the blowfly's head movements during a stabilisation task, and advances our understanding of the underling neural mechanisms.

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Reduced resting state functional connectivity associated with FDG-pet hypometabolism in Alzheimer`s disease

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Background:

In Alzheimer's disease (AD), FDG-PET detected hypometabolism is prominent within the temporo-parietal regions. These brain areas spatially overlap with the default mode network (DMN), which can be detected by functional connectivity (FC) analysis of resting-state fMRI (rsfMRI). Despite the spatial correspondence between FDG-PET and the DMN, the association between FDG-PET and rsfMRI changes is not well understood. Here, we aimed to jointly assess rsfMRI and FDG-PET in AD dementia.

Methods:

27 elderly healthy controls (HC, mean age = 74.6 yrs, SD = 6.33) with normal levels of beta-amyloid (global AV45-PET <1.11) and 25 patients with AD dementia (mean age = 72.18 yrs, SD = 7.5) were assessed within the Alzheimer's Disease Neuroimaging

Initiative (ADNI). For these subjects, scans including FDG-PET, rs-fMRI, and AV45-PET were available. rsfMRI and FDG-PET (normalized to the pons) were spatially normalized to MNI space. On the basis of rsfMRI, regional homogeneity (ReHo) analysis, which determines spatial clusters of synchronous time courses of the BOLD signal, was assessed as a measure of FC. ReHo and FDG-PET were compared between AD and HC using an ANCOVA, controlling for age, gender, and education. Using joint ICA (jICA), we investigated the association between differences in FDG-PET and ReHo changes. Finally, differences in seed-based FC between spatial locations of the peaks of FDG-PET group differences were computed.

Results:

FDG-PET metabolism was reduced in AD patients predominantly within the precuneus, lateral parietal lobe, medial temporal lobe, dorso-lateral prefrontal cortex (DLPFC) and medial PFC (mPFC) when compared to HC. AD patients also showed ReHo decrease within the precuneus, lateral parietal cortex, and mPFC. The jICA revealed that reduced FDG-PET metabolism in AD patients was related to reduced FC within the DLPFC. When using the peak locations of FDG-PET hypometabolism in AD, reduced FC (Pearson moment correlations) were observed within the left middle temporal gyrus and the right Inferior temporal gyrus (FDR p=.05) in AD.

Conclusion:

Temporo-parietal and prefrontal hypometabolism was associated with reduced FC within the prefrontal cortex and parieto-lateral temporal brain regions. These results

suggest that FC changes may underlie metabolic changes; this needs to be further investigated in longitudinal studies.

Indirect activation of the endocannabinoid system: 2-arachidonoylglycerol mediates cannabinoid-dependent effects in a mouse model of temporal lobe epilepsy

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Purpose:

The endocannabinoid (eCB) system serves a key function in regulating neuronal activity. Thus, the eCB system can be considered a putative target for central nervous system diseases including epilepsies. The aim of this study is to investigate if inhibition of the 2-arachidonoylglycerol degrading enzyme, monoacylglycerol lipase (MAGL), has an impact on epileptogenesis and ictogenesis in the kindling model of temporal lobe epilepsy.

Methods:

Male NMRI mice were stimulated electrically once daily via an implanted depth electrode and received injections of the MAGL-inhibitor (n=12, 8mg/kg, i.p.) or vehicle (DMSO:CremophorEL:saline in a ratio of 1:1:18; n=12) sixty minutes prior to each

kindling stimulation to determine whether treatment exerted any enduring effects (Mann-Whitney U test, student's t -test, two-way ANOVA for repeated measurements).

In addition, we aimed to affirm that the observations are cannabinoid type 1 receptor (CB1R) mediated by using MAGL-inhibitor treated conditional CB1R knockout mice (CamK-CB1 KO) along with littermate controls (CamK-CB1 WT, work in progress).

To evaluate an anticonvulsive potential of the MAGL-inhibitor, fully kindled male NMRI-mice (n=10) received vehicle or the MAGL-inhibitor (4mg/kg, 8mg/kg and 16mg/kg) every second day and the seizure threshold was analyzed.

Results:

The MAGL-inhibitor retards the development of generalized seizures ($p=0.0066$) and decreases seizure ($p<0.0001$) and afterdischarge duration ($p<0.001$). Furthermore, seizure thresholds in MAGL-inhibitor treated mice are higher in non-kindled mice ($p=0.0325$), whereas seizure thresholds after kindling acquisition proved to be comparable in both groups ($p=0.8939$).

In fully kindled mice the duration of behavioral ($p=0.0549$) and electrographic seizure activity ($p=0.0962$) was slightly decreased in response to 4mg/kg MAGL-inhibitor.

Conclusion:

The data demonstrate that indirect CB1R agonism can interfere with the development of a hyperexcitable network in the amygdala kindling model, but has only minor

effects in fully kindled mice. Future studies in chronic epilepsy models are necessary to confirm whether the data indicate a preventive potential of CB1R.

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In vivo/in vitro circuit analysis of neuronal circuits in the visual cortex of mice

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Sensory information processing occurs in highly structured cortical circuits that can be altered by synaptic plasticity as a function of learning. Synaptic plasticity can be expressed by either modulating the strength of existing synapses, or the anatomical rearrangement of synaptic contacts, resulting in a rewiring of the neuronal circuit. However, very little is known about the identity of the functional circuit reorganization underlying the plasticity of cortical maps in mouse visual cortex. Moreover, how individual neurons undergo changes in synaptic connectivity during a plasticity paradigm has yet to be investigated. To address this question, we aim to employ a combined in vivo/in vitro approach to directly assess changes in connectivity of neurons, which were functionally characterized in vivo, subsequently using in vitro dual-patch recordings together with circuit mapping by glutamate uncaging.

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A potential regulator of Amyloid precursor protein biogenesis: Thyrotropin-releasing hormone receptor

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Cerebral accumulation and aggregation of Amyloid β-peptide (Aβ) are major pathological hallmarks of Alzheimer disease (AD)[1]. The neurotoxic Aβ derive from Amyloid precursor protein (APP), which shed by β-secretase to generate a C terminal fragment (βCTF) that is the immediate precursor for the subsequent γ-secretase cleavage[2]. Modulation or inhibition of secretases activity is one of the potential therapeutic strategies. Pharmacological inhibition and modulation of these enzymes therefore are considered as important approaches to AD. However both β- and γ-secretase have multiple substrates, thus inhibitors might cause serious side effects[3]. Therefore, potential regulatory steps along the amyloidogenic pathway draw our attention, such as the metabolic fate of APP, βCTF and Aβ. To find such regulators, a genome-wide RNA interference (RNAi) screen in Drosophila S2 cells was performed and revealed 16 novel genes that significantly modified Aβ secretion[4]. TRHR (Thyrotropin-releasing hormone receptor), a G-protein coupled receptor, is one of them. It was identified as a potent modifier of Aβ generation in S2, HEK293 and SH-

SY5Y. Our data show that this phenomenon is attributable to a reduction of APP mRNA and protein.

TRHR siRNA treatment modifies Aβ generation in human neuronal and peripheral cell types. Knockdown TRHR using siRNA from two sources decreases APP mRNA and protein levels, and consequently lowers Aβ secretion. Accordingly, overexpression of HA-TRHR increases APP mRNA and protein levels. This indicates that TRHR expression correlates with APP expression in human cell lines. Rescue experiments further confirmed this relation. RNAi resistant HA-TRHR partially restores APP levels (about 85%) in TRHR knockdowned cells. The partial rescue might due to variations from the transient expression system. Thus, our results indicate that TRHR might regulate APP mRNA in an unknown manner.

Aβ is a central player in AD pathology which is generated from its precursor APP by proteolysis[5]. Therefore by regulating APP transcription or translation, Aβ production may be lowered. In addition, as a G-protein coupled receptor, TRHR may be a valuable drug target. We conclude that TRHR regulates APP mRNA in human cell lines, thus it might be a potential therapeutic target for AD. To further consider its medicinal potential, we must validate this effect in mouse model, as well as study its mechanism.

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Exploring navigational abilities of zebrafish

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Navigation is an important task which different animals need to perform every day: to find the nest or the quickest way to the food source, to explore and control the environment. Experimental studies of navigational abilities of animals progressed significantly after the discovery of place cells in rat hippocampus (O'Keefe and Dostrovsky, Brain research 34, 1971). Since then other types of cells involved in navigation of rodents, e.g. grid cells and head-direction cells, were discovered (Hafting et al., Nature, 2005; Ranck, 1984).

Navigational abilities in animals other than rodents are not as well studied. One of the organisms which has several advantages over rodents for navigational studies is zebrafish. Firstly, zebrafish move in a 3D space of water, and that enables us to study an additional dimension of movements. Secondly, during the larval stage of development zebrafish are translucent. This quality allows for easy noninvasive microscopic access to the brain of the fish larva. In addition, various genetic techniques are available for zebrafish (e.g. Gal4/UAS system (Scott et al., Nat Methods,

2007)), which allow to highlight various types of neurons with fluorescent dyes and track or control neuron activity through time.

Our aim is to look at the brain activity of the fish during navigation using two-photon imaging. Fish's head (but not tail) needs to be immobilized for the imaging. As the fish cannot move, the real environment for navigational task has to be substituted with virtual environment. Virtual reality is presented in front of the fish on the screen and is updated in real time in accordance with movements of fish's tail.

We plan to simulate conditioned place preference task in the virtual reality and perform brain imaging simultaneously. With this method we hope to find cells or groups of cells which are responsible for space recognition and navigation in zebrafish.

The structural spine plasticity is impaired in amyloid precursor protein knockout mice

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Dynamic synapses are the basis of adjusting to changes in the external environment in the adult brain. Synapse formation, elimination and morphological alterations rewire neural circuits. The molecular mechanisms underlying experience-dependent plasticity in the adult brain are still largely unknown. Amyloid precursor protein (APP) is an appealing candidate for synaptic modulation. Besides the intensive studies of the proteolytic processing of APP which may play a central role in Alzherimer's disease, recent studies have suggested APP also participates in normal synaptic formation and funtion[1,2]. The roles of APP in the degree of spine plasticity in adulthood and experience-dependent structural plasticity in adult brain remain unknown. This study shows that in APP knockout (APP-KO) mice, elimination and formation of dendritic spines from cortical layer V pyramidal neurons are both decreased while spine morphology is altered. Enriched environment (EE) exposure does not change the spine

density and morphology in APP-KO mice. Constitutive expression of the secreted APP ectodomain fails to rescue the impaired structural plasticity in APP-KO mice.

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