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Persistence and termination of absence epileptic seizures: the role of striatal feedforward inhibition

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The basal ganglia (BG) are a set of subcortical nuclei involved in various functions e.g. motor control or decision making. BG dysfunctions are responsible for movement disorders such as Parkinson's disease. Recently, the BG have been shown to be involved in absence epilepsy, which is characterized by brief interruptions of consciousness accompanied by abnormal oscillations in the thalamo-cortical complex. Remarkably, during seizures, striatal medium spiny neurons are strongly inhibited by GABAergic interneurons. However, the participation of the BG in the maintenance of absence seizures is still unknown.

Here we hypothesize that absence seizures express a pathological bistability in the dynamics of the BG-cortex network between a normal asynchronous state where MSN are active and an abnormal oscillatory state where MSN are inhibited. We explore this hypothesis in large computational model of the cortico-BG network. We first investigate analytically the dynamics of a rate model of the network and find that it can operate in three regimes of activity: 1) Asynchronous activity 2) Synchronous oscillations 3) Bistability between asynchronous activity and oscillations. These activity regimes depend on the balance between negative and positive BG-cortical feedback loops and on the strength of striatal feedforward inhibition. Using numerical simulations, we show that these regimes and their dynamics transitions are also present in a biologically realistic network of spiking neurons. Importantly, increasing the feedforward striatal inhibition suppresses the MSN activity during the seizures and enlarges considerably the region of bistability. This is because in this conditions the direct pathway is inactivated.

We show that the behavior of our model is consistent with previous experiments showing that pharmacological blockade of the subthalamo-nigral pathway or enhancement of striatal output activity stops the seizures. It also predicts that seizures can be terminated by a transient excitatory input to the cortex with well-defined phase-duration-amplitude relationship. Preliminary experimental results in a well-established genetic rodent model of absence epilepsy confirm this prediction. In particular, successful seizure termination requires that the timing of stimulation within the oscillation cycle falls in a given window as predicted by our theory. In conclusion we argue that an abnormally strong striatal feedforward inhibition can be responsible for a pathological bistability of the cortico-BG network that we identify with absence epilepsy.
Dynactin mutations associated with amyotrophic lateral sclerosis and their effect on axonal transport and neuromuscular junction formation

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Amyotrophic lateral sclerosis (ALS) is an adult-onset neurodegenerative disease, which is mainly sporadic in nature. This progressive pathology has an estimated incidence of 1:1000 and generally leads to death within 2-5 years of diagnosis due to muscle wasting and severe motor neuron loss. Over the last years, mutations have been identified in both sporadic and familial ALS patients, interfering with the function of many genes, including DCTN1, which encodes for a subunit of the motor protein complex component dynactin. The dynactin complex serves as an adaptor for the dynein motor complex, responsible for retrograde axonal transport, and it is believed to regulate dynein activity and the binding capacity for cargos. Interestingly, axonal transport deficits have been reported in various neurodegenerative diseases owing to the fact that neurons are highly polarized cells that depend on active axonal transport for growth, establishment and maintenance of synapses.

Defects in transport of material for development or clearance of detritus in the axon can lead to neuronal stress and cell death and could arise from different causes: preferential type of transport, varying load size, and depletion or dilution of the motor protein populations.

In order to determine how retrograde axonal transport is involved in the pathogenesis of ALS, we are characterizing a mutant zebrafish line for dctn1 with regard to axonal development of primary motor neurons, formation and stability of the neuromuscular junction and the behavioral phenotype produced.

Fast axonal transport defects are quantified in primary motor neurons using the GAL/UAS bipartite system and fusion protein tracking in vivo by confocal timelapse microscopy. We are investigating the transport dynamics of cargos such as endosomes, mitochondria, synaptic vesicles and neurotrophic receptors in the motor neurons of wild-type versus dctn1 mutant embryos in vivo, and over time. The yeast MSN/PP7 system allows us tagging and visualization of target mRNAs as they are transported to the synapse for local synthesis. As dynactin was reported to be essential to synapse stability, we are examining the formation and maintenance of the NMJ by immunohistochemistry (structure), by use of synaptophysin-GCaMP for calcium imaging (function) and we will observe its integrity over time. Behavioral analysis of the mutant embryos will serve as readout of the defects at the motor neuron and NMJ level.

We hope to elucidate key molecular mechanisms in ALS etiology by revealing the role of dynein in NMJ maintenance and identifying novel regulatory events in axon degeneration and muscle atrophy along disease progression.
Poster n°3

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PhD directed by Dr. Marianne DIETERICH
Topic of Thesis: Aging of the vestibular system

**Magnetic vestibular stimulation (MVS) influences fMRI resting-state fluctuations**

*The modulation of the default-mode network as an exemplary case*

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**Synopsis:**
Dizziness in the presence of strong magnetic fields has been noticed ever since the first magnetic resonance experiments at high field strengths ($B_0 > 1$ tesla) have been conducted. Recently it was demonstrated that healthy subjects inside MR machines develop a persistent nystagmus in darkness, while patients lacking bilateral peripheral vestibular function did not show this effect. The aim of our current study is to show that this magnetic vestibular stimulation (MVS) does influence fMRI results. We studied the influence of MVS on fMRI resting-state fluctuations in healthy subjects imaged at 1.5Tesla and at 3Tesla. We found that significant modulation of the default mode network occurs, mainly in areas associated with vestibular function. As proposed for MVS, the modulation scales significantly higher than the expected BOLD signal increase due to $B_0$ without an additional modulation effect. We conclude that MVS does significantly modulate fMRI resting-state networks.

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Physiological recruitment of CSF-contacting neurons: a proprioceptive feedback loop in the spinal cord

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Cerebrospinal fluid contacting neurons (CSF-cNs) line the central canal of the spinal cord, have ipsilateral ascending axon but lack any obvious dendrites. They are conserved across many vertebrates and marked by their expression of GABA and the TRP-channel pkd2l1 which has been associated with responses to changes in pH and osmolarity. Their atypical morphology makes them interesting candidates for sensory cells and optogenetic activation of CSF-Ns can influence swimming behavior. The project aims to investigate the sensory roles and physiological recruitment of CSF-cNs. We use genetically encoded calcium sensors, two-photon imaging, uncaging and electrophysiology to investigate the sensory roles and physiological recruitment of CSF-cNs in zebrafish larvae.
The human brain is able to adjust and exploit multiple strategies for a same task, depending on behavioral demands. The representations of such stimuli-response mapping rules are called task sets. Most of the theoretical research on rule-based behavior is based on computational models at the level of behavior. Little is known however about its neural implementation and mechanisms.

We examine a candidate mechanism for neural implementation of task sets by means of synaptic plasticity. Our model is composed of two interacting neural circuits. The associative network learns one to one associations between visual stimuli and motor responses, but cannot learn more than one stimuli-response mapping. The task rule network learns the representations of those mappings through hebbian and temporal sequence learning mechanisms. Task sets are encoded in its pattern of synaptic connectivity and a feedback to the associative network enables their retrieval.

We first implement a rule-independent associative network. Fitting the model to behavioral data, we find that it can account for behavior in the session in which 24 different task sets are presented one after the other. In contrast, it poorly describes the behavior when only 3 task sets are presented repeatedly across the whole session. Introducing the task rule network permits to account for the data. Hence we show the importance of its activity and of its feedback to the associative network for the retrieval of a previously seen rule. Then we describe the effects of progressive learning through synaptic plasticity in the task rule network.

Our model explores a mechanism for neural implementation of learning, acquisition and activation of rules towards action, at the boundary between functional and neuronal levels.
Detecting emotional patterns associated to visual evoked potentials in EEG

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This work presents an electroencephalogram (EEG) study for the building of an emotion recognition system. The features from EEG signals are classified by considering the subjects emotional responses using information from the frequency spectrum. Therefore, this work investigates the performance of the Correntropy for patterns visualization and the Non-negative Matrix Factorization method in the patterns detection for the frequency analysis on selected signals.

The study was performed to collect 32 channels from the scalp of EEG data, from 4 healthy subjects experiencing 3 emotional states while are exposed to visual stimuli during 30 seconds. The data used for pattern recognition were extracted using Empirical Modal Decomposition.

The proposed method shows results that accurate the brain activity visualization in the scalp for pleasant and unpleasant responses, particularly the lobe where is located the response.
Perceptual and contextual cues for language separation in bilingual infants

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During the first years of life, infants rapidly learn to process speech from a continuous stream, and become able to identify the sounds, words and structure of their native language. Children growing up in a bilingual environment face the additional challenge of having to simultaneously detect and separate mixed language input into two individual systems. In spite of this, language acquisition in bilingual infants seems to develop normally, following approximately the same timeline as in monolinguals. Previous research suggests that infants are sensitive to perceptual information, such as rhythm and facial gestures, which could help them to discriminate the languages. However, the mechanisms and features that are most reliably used by bilingual infants to separate their input remain unclear. In this project we present an interdisciplinary approach to study various perceptual and contextual cues that may guide language separation during the first two years of life, with a particular focus on the role of speakers and context. As an initial step, we are preparing questionnaires for bi/multilingual families in order to measure the distribution of language use as a function of talker and context, as well as evaluating computational language discrimination tools to study phonetic cues. These methods will be combined with behavioral experiments to evaluate the role of these cues in language separation.
Value-based decision-making comprises a range of computations that are partly modulated by activity of dopamine (DA) neurons in the ventral tegmental area (VTA). Mice were housed in a closed economic environment and received their daily food solely through operant tasks involving lever presses. The continuous recording of lever choices and VTA DA neuron activity with in vivo electrophysiology allowed us to investigate the involvement of VTA DA neurons in the computations underlying the processing of effort and uncertainty in decision-making. VTA DA neurons display heterogeneous – excitation and inhibition- activity patterns along the different behavioral events. Furthermore, an increased (>fixed ratio 1) effort requirement encouraged the animals to choose the rewarding option. However, on average WT mice still displayed an exploration rate of 20 percent. This exploitation-exploration trade-off was shifted significantly after chronic exposure to nicotine. Chronic administration of nicotine did not have a significant effect on the sensitivity to uncertainty in the probabilistic discounting task.
Role of perivascular cells in neuro-immune responses to neurodegeneration in Parkinson's disease

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In the field of neurodegenerative diseases (ND), the concept of non-cell autonomous mechanisms suggests that neurodegeneration is not just mediated by damages within the affected neurons but is also influenced by interactions with neighboring glia and peripheral immune cells. This so-called neuroinflammatory response produces culprits that could be at the core of the progressive nature of many ND. It was previously reported that in Parkinson disease (PD) CD4+ T cells infiltrate the brain and have a deleterious influence on dopaminergic neurons (DN) from the Substantia Nigra, the main degenerating population in PD. It was shown that the extravasation of CD4+ T lymphocytes was cell and region specific, highlighting the active role of the blood-brain barrier (BBB) in the process. In this context, our central hypothesis is that pericytes and perivascular macrophages, strategically positioned within the BBB, actively participate in the infiltration process and the consequent degeneration of DN. Through genetic fate mapping and specific cell ablation approaches the project will provide a more complete picture of the role of two neurovascular unit members in Parkinson-like degeneration, highlighting potential therapeutic strategies based on BBB modulation.
The role of the β4 nicotinic acetylcholine receptor subunit in nicotine addiction

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Nicotine is the chief neuroactive compound in tobacco that drives its repeated consumption by activating neuronal nicotinic acetylcholine receptors (nAChRs). The receptor is a transmembrane pentameric ligand-gated ion channel found in the central nervous system, composed of α, or α plus β subunits (α2-10 and β2-4). Using transgenic mouse lines, lentivirus technology and behavioural assessment, we show that β4* nAChRs are required for intravenous nicotine self-administration (7.5-60 µg/kg/infusion), and that β4 regulates basal and nicotine-induced meso-accumbal activity. Targeted re-expression of β4 in the medial habenula on a knock-out (KO) background partially restores the nicotine self-administration deficit observed in KOs. In vivo electrophysiological assessment demonstrates that IPN β4* nAChRs regulate the ventral tegmental area’s sensitivity to nicotine. Furthermore, preliminary data suggest that IPN β4* nAChRs also contribute to nicotine self-administration. We therefore show that β4* nAChRs contribute to chronic, voluntary nicotine consumption, and that the habenulo-peduncular pathway is able to regulate meso-accumbal activity integral to this behaviour.
Role of complement system-related genes in synapse formation and specificity in the olivocerebellar network

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Our aim is to identify signaling pathways that control synapse formation and specificity in neuronal networks. Using a comparative transcriptomic analysis in the olivocerebellar network, we have found that amongst Purkinje cell (PC) afferents, Inferior Olivary Neurons (ION) have a significantly higher representation of immune-system related genes compared to Granule Cells (GC). These include genes coding for both innate and adaptive immunity-related pathways. Interestingly, the two inputs code for different members of the family of complement proteins.

This suggests that the differential expression of immune system-related genes in the ION and GC confers a molecular identity, thereby playing a role in specifying their non-overlapping synaptic innervation territories on PCs. In particular, we are focusing on two complement system-related proteins, C1ql1 and Susd4, that are highly expressed by IONs during development. Our expression and functional analysis suggest that both C1ql1 and Susd4 promote CF/PC synapse formation, but only C1ql1 defines CF territory on the PC dendrites. To provide a complete understanding of their role in the establishment of PC connectivity, we need to determine whether C1ql1 and Susd4 cooperate to control network formation.
Is the visual cortex exclusively visual? The engagement of the visual cortex in tactile Braille reading in the sighted examined with fMRI, rsMRI and TMS

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Reading Braille in congenitally blind subjects activates the Visual Word Form Area (VWFA), a region in the lateral occipital cortex, known to develop expertise for reading in sighted (Reich et al., 2011). This surprising finding challenges the canonical, sensory-based (visual, tactile...) division-of-labour in the brain. To further investigate this results, we decided to check which brain regions would activate when sighted readers, who lack the large-scale plasticity that appears in blind’s visual system, read Braille. 29 subjects enrolled in a 9 month long, made-to-measure Braille reading course and two identical functional and resting-state MRI experiments performed before and after the course. Experimental tasks included reading regular visual words, Braille dots presented visually (visual Braille) and tactile Braille. Additional TMS examination was performed on 12 participants after the course.

All subjects progressed in tactile reading across the course. After the course reading by touch activated the VWFA and other left occipital regions. The activity of VWFA increased during the training and this increase was specific only for tactile Braille. Additionally, we found no change in the somatosensory areas resulting in the course. The only brain region that correlated with individual tactile Braille proficiency was the inferior occipital gyrus. The RS-fMRI showed increased functional connectivity between the VWFA and the somatosensory areas. TMS to the VWFA resulted in reduced reaction time for tactile Braille words during a lexicon decision task.

We show that a complex tactile task, such as Braille reading, activates a purely “visual area”, the VWFA, and does not cause any changes in the activation in somatosensory cortices. Thus, our results challenge the canonical view of a sensory-specific cortical division-of-labor (vision in the visual cortex; touch in the somatosensory cortex, etc.). This study together with previous studies on metamodal cognition suggest that the dominating, sensory-based theory of brain organization requires a major revision.
Mapping oxygen partial pressure in the awake mouse brain

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Two-photon phosphorescence lifetime microscopy (2PLM) has been recently used for depth-measurements of the oxygen partial pressure (Po2) in the rodent brain. In capillaries of olfactory bulb glomeruli, 2PLM has also allowed simultaneous measurements of Po2 and blood flow, and revealed the presence of erythrocyte-associated transients (EATs), i.e. Po2 gradients associated with individual red blood cells (RBC). We recently examined EAT properties in olfactory bulb capillaries in anaesthetised mice, and found that at rest, Po2 at EAT peaks overestimates the mean Po2 by 26 mm Hg. In addition, we found that the inter-RBC Po2 is at equilibrium with and thus reports Po2 in the neuropil [1]. However, anaesthesia has profound effects on blood flow and neuronal activity and thus the levels of vessel and tissue oxygenation. We have compared Po2 maps in the olfactory bulb superficial layers under isoflurane anaesthesia and in awake, unstressed, head-fixed mice. We report that under isoflurane anaesthesia (0.7-0.8%) there is a significant elevation in RBC flow, and an associated increase in capillary mean Po2, Po2 at EAT peaks, and inter-RBC Po2 (and thus tissue Po2), when compared to the awake state. We then investigated O2 distribution at rest in the somatosensory cortex. We show that in contrast to previous reports, no gradient of Po2 exists in penetrating vessels with increasing depth in the cortex. We also examined capillary and local tissue Po2 in layers I, II/III, and IV, showing that Po2 in layer I is significantly lower than that in layer II/III and IV, and no Po2 gradient exists within layer II/III and layer IV. Additionally, we are currently examining the relationship between RBC flow and EAT properties and the rate of oxygen extraction from capillaries in these different cortical layers, along with the relationship between branching order and vessel and tissue Po2.

Cortical Foxp2 modulates ultrasound vocalizations and social behavior in adult male mice

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The transcription factor FOXP2 has been implicated in speech and language development. The neuronal expression patterns of FOXP2 are highly similar across different vertebrate species, suggesting conserved roles in neural circuits underlying social cognition and behavior. In the cortex, Foxp2 is expressed in deep layer pyramidal cells. Current data support a role for Foxp2 in corticostriatal circuitries involved in motor control, however specific functions of Foxp2 in the cerebral cortex and its role in cognitive and behavioral traits are largely unknown.

To investigate the role of Foxp2 in the cortex we generated Nex-Cre Foxp2²loxP/loxP mice (cKO), thus restricting Foxp2 deletion exclusively to pyramidal neurons of the dorsal telencephalon.

While development and basic adult behavior of cKO mice were normal, screening for more complex social behavioral traits in a resident-intruder paradigm showed changes in male-male interactions. An automated screening approach revealed a significant decrease in following and close contact interactions together with an increase in oral-genital contacts initiated by WT intruders.

Mouse ultrasound vocalizations (USVs) are believed to have a communication role and are frequently emitted during social interactions. We have recorded and analyzed USVs during social contacts in resident-intruder tests and observed differences in the structure of male vocalizations in male-male and male-female interactions. Social (male-male dyads) USVs are altered in structure and possibly in low-frequency power of simple calls, while courtship vocalizations (male-female dyads) show anomalies in the range and fraction of complex calls. Recordings of female-female interaction USVs did not reveal alterations.

Together, these findings suggest that cortical Foxp2 may be involved with fine-tuning pitch and structure of mouse vocalizations. In addition, cortical Foxp2 seems to affect social approach behavior of cKO males. Further experiments will explore the ecological significance of these parameters.
The impact of power postures on self-relevance appraisal during emotion recognition

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Consistent with the theory of embodiment, personal needs and goals are closely associated with body states. Along with characteristics of social signals, like emotion and gaze direction, an individual's body state plays a crucial role in determining what they perceive as self-relevant. Typically, angry facial expressions are appraised as more relevant with direct gaze, while fearful expressions are considered more relevant with averted gaze. Previous studies of our team have shown that power-related body postures impact on this process of self-relevance appraisal during implicit emotion processing. The present study extends these findings to explicit emotion recognition. 70 participants adopted either a high- or a low-power posture before performing a categorization task on angry and fearful emotional expressions, presented with direct or averted gaze. In each posture group, the effect of gaze on emotion discrimination occurred only for the more self-relevant emotion, as determined by power level: anger in the high- and fear in the low-power group. In low-power men, however, the self-relevance effect was preserved for both emotions. These findings demonstrate that the body posture of the perceiver crucially impacts on his explicit emotion discrimination ability. Since the postures are suggested to elicit testosterone and cortisol responses which could underlie the changes in emotion processing and the observed gender difference, a next experiment will attempt to characterise the time course of these hormone responses.
Neural Precursors Derived from Mouse iPS Cells Extensively Remyelinate the Demyelinated Central Nervous System

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Objective: Induced pluripotent stem cell-derived neural precursor cells (iPSC-NPCs) were developed recently from reprogrammed cells. However, the repair efficacy and safety of these cells in demyelinating conditions, remain to be well addressed. In this study, we fully characterized mouse iPS-NPCs (miPS-NPCs) in vitro and in vivo after transplantation in models of adult demyelination and compared side-by-side their repair efficiency to embryonic mouse brain NPCs (mE-NPCs).

Methods: mE-NPCs as control and miPS-NPCs were derived from Sox2 knock-in mice and characterized for their expression of markers of immature or mature neural cells. To investigate the behavior of these cells in demyelinating conditions, we induced focal demyelination injecting lysolecithin in the spinal cord of adult dysmyelinated shiverer or nude immunodeficient mice. Cells were transplanted in the lesion site 48 hours after demyelination and animals sacrificed 1, 2, 6 and 10 weeks post graft to assess survival, migration and differentiation potential of the grafted cells. Functional recovery was evaluated by recording of somatosensory evoked potentials.

Results: miPS-NPCs expressed the immature markers of naturally committed NPCs in vitro at the protein and transcriptional levels. Transplantation of miPS-NPCs in demyelinating conditions revealed their capacity of survival, integration, extensive migration and timely differentiation from immature to mature oligodendrocytes. Grafted miPS-NPCs generated extensive and compact myelin around host axons, restoring nodes of Ranvier and conduction velocity with the same efficacy as mE-NPCs. Tumor following engraftment was never observed.

Interpretation: Thus miPS-NPCs differentiated successfully into bona fide mature remyelinating oligodendrocytes outcompeting endogenous cells for myelin repair and behaved as efficiently as naturally committed NPCs. These novel insights into the biology of iPS-derived NPCs should help establishing the pertinence of their use for regenerative biomedicine of CNS myelin diseases.
Introduction
Stromal derived-cell factor 1 (SDF1, CXCL12)-mediated activation of the chemokine receptor CXCR4 is involved in developmental and pathologic processes, including primordial germ cell migration, invasive migration of cancer cells and neutrophil retention in bone marrow, while mutations in CXCR4 are associated with neutropenia. Here, we provide evidence for a role of SDF1/CXCR4 signaling in neutrophil motility during inflammation and resolution.

Materials and Methods
We used mutant zebrafish larvae carrying functionally null versions of SDF1a (medusa) and CXCR4b (odysseus). Neutrophils were visualized with Sudan Black staining or by using transgenic zebrafish whose neutrophils express GFP (TgBAC(mpx:GFP)). Inflammation was induced by tail transection of larvae and recruited neutrophils were quantified during inflammation and after its resolution. In vivo time lapse microscopy was carried out in larvae subjected to tail transection, and neutrophil dynamics during inflammation was studied.

Results
Mutant larvae show significantly less granulocytes in the hematopoietic tissue and a progressive increase of circulating neutrophils. Quantification of neutrophils recruited after tail transection shows a significant increase of infiltrating cells and diminished clearance in mutant larvae compared with their siblings. Time-lapse microscopy of neutrophil recruitment after tail transection shows increased directionality of these cells to wounds in mutants.

Discussion
We provide evidence for a role of SDF1a/CXCR4b signaling in neutrophil recruitment and clearance during inflammation and its resolution, respectively. Our results support SDF1a as a retention signal for neutrophils in the hematopoietic tissue, restricting the number of responding neutrophils upon tissue injury.

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The visual system generates representations of visual information from elementary features in the retina up to complex objects in the anterior temporal cortex. However this processing comes at a cost, namely that of discarding information along the way. The aim of the project is to investigate how ocular dominance and disparity tuning maps from two eyes interact to form stereo perception during the visual stream processing and to provide computational model for the phenomena.

The main convenience of a ferret as an animal subject to study binocularity is a possibility to access simultaneously with great time resolution activity from a population of primary and secondary visual cortex cells (areas 17,18, 19 and 21) with multielectrode array technique. Huge receptive fields of the cells in ferret visual cortex and smooth maps of disparity, ocular dominance etc. are important advantage. Finally, ferret is a binocular animal that can be used for head-fixed awake recordings during stereo visual stimulation and thus both electrophysiological and behavioral responses about 2D or 3D perception could be obtained with exact coordinates of the stimulus on the visual cortex surface.

Overall, this integrative project between behavior, electrophysiology and computational modeling should improve our understanding of processing in the visual cortex.
Novel IL1RAPL1 mutations associated with intellectual disability impair synaptogenesis

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Mutations in interleukin-1 receptor accessory protein like 1 (IL1RAPL1) gene have been associated with nonsyndromic intellectual disability (ID) and autism spectrum disorder. This protein interacts with synaptic partners like PSD-95 and PTPδ, regulating the formation and function of excitatory synapses. The aim of this work was to characterize the synaptic consequences of three IL1RAPL1 mutations, two novel causing the deletion of exon 6 (Δex6) and one point mutation (C31R), identified in patients with ID. Using immunofluorescence and electrophysiological recordings, we examined the effects of IL1RAPL1 mutant over-expression on synapse formation and function in cultured rodent hippocampal neurons. Δex6 but not C31R mutation leads to IL1RAPL1 protein instability and mislocalization within dendrites. Analysis of different markers of excitatory synapses and sEPSC recording revealed that both mutants fail to induce pre- and post-synaptic differentiation, contrary to WT IL1RAPL1 protein. Cell aggregation and immunoprecipitation assays in HEK293 cells showed a reduction of the interaction between IL1RAPL1 mutants and PTPδ that could explain the observed synaptogenic defect in neurons. However, these mutants do not affect all cellular signaling because their over-expression still activates JNK pathway. We conclude that both mutations described in this study lead to a partial loss of function of the IL1RAPL1 protein through different mechanisms. Our work highlights the important function of the trans synaptic PTPδ/IL1RAPL1 interaction in synaptogenesis and as such in ID in the patients.
C-terminal tail of transmembrane BMP receptor type II localize at the cell nucleus, binds to DNA and modulate morphological differentiation of motor neuron-like cells

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Introduction: BMP receptor type II (BMPRII) is a transmembrane protein receptor characterized by a long intracellular C-terminal tail that is not required for canonical signaling. We have found a C-terminal fragment of BMPRII in the nucleus of mouse motor neuron-like NSC-34 cells. Also, we have found that BMPRII is up-regulated upon differentiation of these cells. Our main aim is analyze the possibility that this C-Tail fragment interact with DNA strains and explore the potential role of this C-terminal tail in motor neuron differentiation.

Materials and Methods: We prepare NSC-34 enriched nuclear cell fractions and evaluated the C-terminal tail release from DNA by using DNase and NaCl treatment. Subsequently, we performed Western Blot analysis against C-terminal Tail of BMPRII and against Histone H1. Furthermore, to evaluate the role of BMPRII C-tail in morphological differentiation of these cells, different constructions of human BMPRII GFP-tagged at the C-terminal were transiently transfected and live cells were visualized by fluorescence microscopy.

Results: DNase treatment, which digests uncompact DNA strains, showed a concentration-dependent decrease of BMPRII C-Tail in enriched nuclear cell fractions with a concomitant release in the supernatant. Disruption of DNA/protein interaction by NaCl treatment also induces a C-Tail decrease in enriched nuclear cell fractions and its appearance in the supernatant. On the contrary Histone H1 was not significantly released. Moreover, NSC-34 cells transiently transfected expressing a full form of BMPRII (1031 aac) showed reduced morphological differentiation. On the contrary, cells expressing a short form of BMPRII (lacking 400 C-terminal aac) showed a differentiation similar to control cells. Besides, cells expressing a C-terminal tail of BMPRII (last 300 aac) showed a noticeable stain at the cell nucleus both in growing and differentiation conditions, and a reduced morphological differentiation.

Discussion: Our evidence suggests that C-terminal tail of BMPRII interacts with unpacked DNA at the cell nucleus and also suggest that the C-terminal tail of BMPRII contains at least one Nuclear Localization Signal. This localization at the cell nucleus could be modulating negatively motor neuron morphological differentiation and represents the first step to propose a role in gene activity regulation by this protein fragment in motor neuron-like cells.

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NG2-glia - also known as oligodendrocyte progenitor cells (OPCs) - are the only proliferating cells in the adult brain parenchyma constituting a major cell fraction (5-10%) of the brain. Despite their high number and substantial characterization, very much remains unclear regarding their physiological function. To address this question, we used conditional genetic deletion of the Esco2 protein, that triggers apoptosis of dividing cells during M-phase, in the inducible Sox10 iCreERT2xCAGeGFPxEsco2fl mouse line (Simon et al. 2012, Whelan et al. 2012), to specifically ablate proliferating NG2-glia in the adult brain.

We could show that deletion of Esco2 in NG2-glia induced ongoing NG2-cell death in the recombined cells that was compensated by the enhanced proliferation of non-recombined cells. Specifically in the white matter (WM) of the cerebral cortex, we could observe a decreased number of newly generated oligodendrocytes and structural changes in the nodes of Ranvier. Interestingly, these animals in contrast to control littermates developed progressive motoric deficits.

As proliferation of NG2-glia is >15 fold increased at 3 days after stab wound injury (3dpl; 3 days post lesion; Simon et al. 2011), we additionally analyzed the role of NG2-glia after acute lesion by ablating them in the above described Esco2-mouse model. Indeed, we could find a transient reduction of NG2-glia around the lesion site within 14 dpl that significantly influenced the reaction of microglia, infiltrating immune cells and astrocytes. Our data suggest that NG2-glia are important for the maintenance of myelin associated structures in the physiological as well as for the injury-related reaction of glial cells in the pathological brain.
Biogenic amine receptors expressed in Drosophila Mushroom Bodies inhibit motor programs

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Several evidences point out the Mushroom Bodies (MB), an important association area in insect brain, as a region that plays a modulatory role on motor programs. As in vertebrates, biogenic amine (BA) systems in the CNS participate in motor control in Drosophila. Therefore it is possible to suggest that BA systems participate in the control of motor programs by modulating the activity of MB. The main objective of this work is to evaluate the contribution of dopamine (DA), octopamine (Oct) and serotonin (5-HT) receptors expressed in MB on motor behavior in fly larva. Locomotion was evaluated in Drosophila larvae (3rd instar) using an automated tracking system. RNAi for the different BA receptors were expressed in MB by means of the GAL4-UAS technique. In order to determine the role of those neurons on neurotransmission, we used an optogenetic tool by expressing a light-sensitive cation channel channelrhodopsin-2 (ChR2) on MB neurons. Our data show an increased locomotion in animals expressing an RNAi for dDA1R, DopR2, OctB1R, Oct-Tyr R, 5HT1AR, 5HT1BR and 5HT2R pan-neuronally. This increase is also observed when the RNAi for dDA1, OctB1R, Oct-Tyr R and 5HT2R are expressed in the whole MB or specifically in the MB gamma-lobe. On the other hand, a decreased motor output is observed expressing the RNAi for OAMBR either in the entire MB neuronal population or in the gamma-lobe. Expression of the RNAi for these receptors in alpha'/beta'-lobe does not have an effect on locomotion. ChR2 expression on gamma-lobe neurons of MB neurons modify the motor activity of fly larvae, whereas their expression on alpha'/beta' lobe does not change locomotion.

These data show for the first time those BAs receptors expressed in MB differentially modulate locomotion in fly larvae. Also, these data suggest that this response is mediated by an inner structure in larval MB, the gamma-lobe.
Poster n°23

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**Reward maximization and effort minimization learning are differentially affected by dopaminergic treatment**

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Previous studies have established the role of dopamine as a major neuromodulator in the reward-based learning and decision making. Specifically, it has been shown that treatment with dopamine precursor L-DOPA enhanced learning from rewards and dampened learning from punishments in patients with Parkinson disease (PD) tested ON and OFF dopaminergic medication. While low levels of dopamine were shown to diminish subject’s willingness to work for the rewards, less is known about how it affects effort-based learning.

We will present new data from patients with PD who performed an instrumental probabilistic learning task in ON and OFF dopaminergic medication states. Subjects had to learn by trial and error how to minimize their physical efforts and to maximize their monetary gains. Preliminary results showed an interaction between learning and medication state. While reward learning was enhanced by dopaminergic treatment, effort learning stayed unaffected by L-DOPA.

We will present further analysis and computational modelling.
Establishing the functional role of spontaneous activity of cerebrospinal fluid-contacting cells in the development of the spinal cord

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Spontaneous activity is a key feature of the developing nervous system and is critical for proper development of neural networks. In the embryonic zebrafish spinal cord, motor neurons from the left and right hemicords alternate rhythmically from 17 hours post-fertilization (hpf) through embryonic development. Cerebrospinal fluid-contacting neurons, also known as Kolmer-Agduhr cells (KAs) are GABAergic and have high levels of spontaneous activity but do not participate in the rhythmic activity of the spinal cord. We characterized the activity of KAs with genetically-encoded calcium indicators and electrophysiology. Using TALEN-mediated mutagenesis, we generated a mutant for TRP channel pkd2l1 and found that spontaneous activity in KAs was abolished, implicating pkd2l1 as a major contributor to embryonic spontaneous activity in these cells. Ongoing work is focused on testing the role of this activity and of GABA release on neuronal specification, axonal guidance, and synaptogenesis in the spinal cord.
On local origins of local-field potentials

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We investigated the spatial patterns in local field potentials (LFP) recorded using Utah array (NeuroPort). To this end, we calculated correlations between spontaneous LFP signals in all pairs of electrodes and classified them into "correlation domains" using various clustering techniques. We found that the signals form coherent spatial structure with multiple domains whose typical size was about 1 mm. Similar structure was observed across subjects and species, but the exact spatial configuration was specific to each subject. To gain insight on the origin of such correlations, we also analysed spatial organization of unit activity. Similar structure was also present in the units, but with smaller domains and larger amount of noise, probably due to coarse sampling of the active neural population. We speculate that these LFP and unit patterns might reflect intrinsic functional connectivity and they might represent the microscopic equivalent of the default mode networks.
Origin of the ‘kink’ of somatic action potentials

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The Hodgkin and Huxley (1952) model of action potential (AP) generation accounts for many properties of APs observed experimentally and has been successfully used in modelling neurons of different types. In this model, however, the spike onset is much slower than in the experimental recordings from the soma. To explain the origin of the observed sharpness (‘kink’) in the spike onset three hypothesis were proposed:

1. Cooperative hypothesis: sodium channels cooperate in the axon initial segment, which makes their collective activation curve much sharper [Naundorf et al., 2006].

2. Lateral current hypothesis: spikes are initiated in the axon and backpropagate to the soma. The kink is caused by the sharpening of the axonal spike by active conductances during its backpropagation through the axon [Yu et al., 2008]

3. Compartmentalization hypothesis: the kink comes from distal initiation and the current sink caused by the difference in the size of the soma and axon [Brette, 2013].

By means of computational modelling and theoretical analysis we investigated lateral current and compartmentalization hypotheses. In order to differentiate those hypotheses, we varied systematically the morphology of the neuron and distribution of the ionic channels along the cell, and tested how they contribute to the appearance of the kink. Preliminary results suggest that the kink at spike onset is primarily due to compartmentalization rather than to active backpropagation.

References


Medium Spiny Neurons (MSN) control the initiation of voluntary movements, promoting the execution of certain motor actions while preventing unnecessary ones. This role is achieved by the parallel action of two MSN subtypes: D1 MSN promote movement initiation while D2 MSN inhibit motor activation. Achieving the correct specification of MSN subtypes is essential for brain functioning; however, it is still largely unknown how this process is regulated during development.

FACS-sorting experiments and full-knockout analysis established that the transcription factor Ebf1 (Early B-cell factor 1) is required for generating subsets of D1 MSN. However the cell-autonomous roles of Ebf1 remain largely to be deciphered. Here we have taken advantage of genetic targeting of MSN subtypes and Cre-Lox recombination to conditionally delete Ebf1 in all MSN or only D1 MSN and analyze how this deletion affects MSN developmental dynamics at both cellular and population scale. Our results provide novel insights on the way transcription factors act at different levels to determine the binary choice between neuronal subtypes and their integration in the brain circuitry.
A role for inter-regional neuronal reactivation and oscillatory events in memory consolidation

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There is evidence that memory consolidation involves communication between the hippocampus and cortical areas such as the medial prefrontal cortex (mPFC). A substantial part of this process is thought to occur during slow wave sleep (SWS). Chronic electrophysiological recordings in rodents have shown that neuronal sequences established during behaviour are reactivated in subsequent SWS, and this has been associated with certain SWS oscillatory events (such as hippocampal sharp-wave ripples, neocortical delta waves and thalamocortical sleep spindles). This project aims to investigate the interplay of neuronal reactivations in the hippocampus and the mPFC, and its fine temporal relationship with SWS oscillatory events after learning.
General principles governing the development of tectal neurons receptive fields in the zebrafish larva

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During development functional properties of visual neurons are highly plastic, undergoing progressive refinement before reaching a mature state. However, despite the large and continuous neurogenesis processes, developing organisms need to maintain stable neuronal representation of object features (position, size or motion direction) to perform relevant visually guided behaviors. Here we asked what are the governing principles that rule the development of visual properties of tectal neurons at the population level.

For that purpose, we used two-photon calcium imaging of HuC:GCaMP5G zebrafish larvae to study the stability and dynamics of receptive fields (RFs) and direction selectivity (DS) changes of large neuronal ensembles in the optic tectum (up to ~500 neurons). The experiments were performed in developing 6-7 days post fertilization (dpf) larvae every 4 hours for a period of up to 12 hours.

Preliminary results obtained at single time points indicate that tectal neurons that are sensitive to discreet portions of the visual field displayed robust RFs (low variance across trials). Conversely, neurons that were close to the neurogenic sites of the OT showed variable RFs across trials and their RFs were not tuned towards specific regions of the visual field (non-single gaussian multimodal RFs).

Our working hypothesis is that cells displaying robust RFs already underwent synaptic pruning and posses few strong synaptic connections. On the contrary, neurons with variable responses (immature neurons) posses numerous weak synaptic connections. Ongoing studies will shed light on neuronal principles underlying the maturation of functional neuronal properties (RFs and DS) along the development of the visual system.
Working Memory – A Truly Conscious Process?

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Working memory (WM) describes the temporary maintenance and manipulation of internal representations. Historically, WM has been regarded as inextricably linked with consciousness (Baars & Franklin, 2003; Baddeley, 2003; James 1890), involving not only a similar network of brain regions, but also the ability to accurately report their contents. Recent evidence, however, questions this view. Consciousness may neither be compulsory for WM, nor may all of the contents of WM be directly reportable (Soto, Mäntylä, & Silvanto, 2011; Dutta et al., 2014; Soto & Silvanto, 2014). Instead, it seems possible that information can be maintained for several seconds outside the realms of awareness and that, as such, an unconscious WM (uWM) system may exist.

We here sought to exploit behavioral and neural data in order to further characterize this novel phenomenon and better understand its relationship with WM. Specifically, we ran two behavioral experiments in conjunction with a magneto-encephalography/electro-encephalography (MEG/EEG) study in healthy human subjects who performed variations of a paradigm in which, after a variable delay, the position and visibility of a masked target had to be rated. Preliminary results support the notion of an uWM system: First, in all three experiments, even when not having seen the target, participants reported the correct target location on significantly more trials than would be predicted by chance alone. Distractor, delay, and load effects, similar to the ones typically expected for WM, were observed and this blindsight performance remained above chance even when asking to manipulate the unconscious information (i.e., report a rotated target location). Second, as indicated by preliminary decoding analyses during the WM delay period, the neural code for a consciously perceived target appears to be much longer-lasting and stable than the one for an unconsciously perceived target. These data suggest that an uWM system, whose effects go beyond those typically observed in priming studies, may indeed exist and thus pave the way for exiting, new research.
Release of glutamate and ATP induced by optogenetic activation of astrocytes

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Astrocytes are endowed with the capability of releasing transmitters (gliotransmitters) among which glutamate, D-serine, ATP, GABA and glycine have been identified. However, whether all astrocytes release these transmitters remains unclear. Moreover, the mechanisms and conditions leading to gliotransmitter release are still highly debated. We therefore aimed at using optogenetic activation of astrocytes to understand better gliotransmission and its consequence on neuronal activity.

We crossed Cx30-cre-ERT2 (kindly provided by Frank W Pfrieger) and Floxed-ChR2-EYFP mice (Ai32; Jackson lab) to induce the selective expression of ChR2 in astrocytes. We first confirmed by immunocytochemistry that EYFP was specifically expressed in the vast majority of hippocampal and cortical astrocytes 21 days after an i.p. injection of tamoxifen. We also used acute hippocampal slices to characterize the membrane currents induced in astrocytes by blue light stimulations of variable duration. At a holding potential of -90 mV, light stimulation induced a fast inward current that peaked in few milliseconds (ms). If light was maintained, this initial peak was followed by a plateau of lower amplitude and, after tens of ms, by a slowly increasing inward current that could last several seconds. We then recorded CA1 pyramidal cells to analyze the neuronal consequences of light-induced activation of ChR2 in astrocytes. We did not observed changes in neuronal membrane currents for short duration, full field, blue light stimulations. Yet, light pulses of more than 1 second reliably induced a sequence of depolarizing-hyperpolarizing responses that were not blocked by TTX (1 µM). The hyperpolarizing current was abolished by the adenosine A1 receptor antagonist DCPCX (200 nM), suggesting a release of ATP or adenosine by astrocytes. The depolarizing component was fully blocked by antagonists of NMDARs (50 µM D-AP5, 40 µM MK-801, 50 µM 7Cl-KYN) but not by the AMPA-KAR antagonist NBQX (10-20 µM). This NMDAR-mediated current was potentiated by the blocker of glutamate transporters TBOA (100 µM) but not affected by application of glycine or D-serine, which in our conditions failed also to induce any change in the baseline membrane current. These results suggest that activation of ChR2 in astrocytes also induces the release of glutamate that targets specifically NMDARs. Pharmacological manipulations indicated that neither GluN2A nor GluN2C/2D contribute to the composition of these receptors. However, the GluN2B selective compound, Ro25-6981 (300 nM) enhanced the light-induced NMDARs currents, indicating a contribution of GluN2B containing receptors activated by a low concentration of glutamate. Finally, the antagonists of purinergic P2 receptors MRS 2179 (10 µM) and PPADS (100 µM) reduced light-induced NMDAR-mediated responses, suggesting that astrocyte release of glutamate was potentiated by autocrine release of ATP activating P2Y1 receptors. These results indicate that activation of ChR2 expressed by astrocytes induces the release of glutamate and of ATP. This release of gliotransmitters leads to the activation of NMDARs, probably extra-synaptic, and of A1 receptors, after degradation of ATP into adenosine, expressed by CA1 pyramidal cells.