THE SECOND NORDIC NEUROSCIENCE MEETING

A scientific meeting for all neuroscientists arranged in Stockholm, Sweden. A wish of achieving greater knowledge about the work done in Nordic institutes to open more interactions with neighboring countries and establish networks for future collaborations.
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*A whole-brain atlas of inputs to inhibitory and excitatory neurons in prefrontal cortex* | Wednesday June 7 - 1430-1630            |
| A17    | 17    | Zakaryah Abdulkarim | - Z. Abdulkarim, H. Ehrsson  
*Recalibration of hand position sense during unconscious active and passive movement* | Wednesday June 7 - 1430-1630            |
| A18    | 18    | Alexey Pospelov | - K. Kaila, A. Pospelov, M, Puskarjov, A. Yukin  
*The brainstem as an independent generator of febrile seizures* | Wednesday June 7 - 1430-1630            |
| A19    | 19    | Poster Retracted | | Wednesday June 7 - 1430-1630            |
*Electrophysiological and molecular comparison of telencephalic interneurons using PatchSeq* | Wednesday June 7 - 1430-1630            |
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<td>Claire Kelly</td>
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<td>Flavio Donato</td>
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<td>Ilary Allodi</td>
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<td>Lilian Kisiswa</td>
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<td>A27</td>
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<td>Maria Jose Lagartos</td>
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  *Revisiting the neurotrophic theory: differential survival capacity of developing sensory neurons* | Wednesday June 7 - 1430-1630 |
  *Intrinsic properties of the serotonergic system development and respiratory network activity in NECDIN-knockout mice: implication for Prader-Willi Syndrome* | Wednesday June 7 - 1430-1630 |
| A33    | 33    | Chiara Ciriachi | - C. Ciriachi, A.B. König, U. Gether M. Rickhag  
  *Chemogenetic inhibition of direct pathway neurons in dorsomedial striatum reduces locomotor activity in mice supporting the role of the direct pathway in promoting movement* | Wednesday June 7 - 1430-1630 |
| A34    | 34    | Daichi Suzuki | - D.G. Suzuki, A. Kardamakis, T. Wibble, J. Peréz-Fernández, S. Grillner  
  *Toward elucidation of a visual decision-making mechanisms: Insights from the lamprey tectum* | Wednesday June 7 - 1430-1630 |
| A35    | 35    | Debora Ledergerber | - D. Ledergerber, R. Gardner, H. Ito, E. Moser, M-B Moser  
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| A36    | 36    | Diana Fernandez Suarez | - D. Fernandez-Suarez, C.F. Ibanez  
  *Genetic inactivation of GFRα1 in the medial habenula of adult mice results in altered anxiety and fear related behavioral responses* | Wednesday June 7 - 1430-1630 |
| A37    | 37    | Eelke Snoeren | - P.T. Huljgens, R. Heijkoop, E. Snoeren  
  *The role of glutamatergic medial amygdala neurons in male rat sexual behavior* | Wednesday June 7 - 1430-1630 |
  *Perineuronal nets in the lateral secondary visual cortex are essential for remote visual fear memory* | Wednesday June 7 - 1430-1630 |
| A39    | 39    | Eric Herlenius | - E. Herlenius, D. Forsberg, G. Drevin and N.J. Pejovic  
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| A40    | 40    | Hoseok Kim | - X. Wang, D. Kaping, I. P. Dorocic, Y. Xuan, M. Parent, N. Karadag, K. Meletis, M. Carlén  
  *Serotonergic DRN neurons directly control impulsive behaviors* | Wednesday June 7 - 1430-1630 |
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<td>Role of Activin-Like Kinase 4 receptor in behavioral sensitization to cocaine</td>
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<td>Neurotransmitter identity and projections of raphe serotoninergic neurons in the zebrafish</td>
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<td>Evaluation of MAP-kinase Interacting kinases as pharmacological target in rodent models of autism</td>
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<td>Coding of impulsivity, reward and attention in the medial prefrontal cortex of the mouse</td>
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<td>Mapping the cocaine induced c-fos activation and inactivation in the mouse brain</td>
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<td>Vectorial representations of discrete landmarks in the medial entorhinal cortex</td>
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<td>Uppsala University Behavioral Facility (UUBF) has the capability and competence to conduct behavioral studies in mouse, rat and fish</td>
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| B21    | 21    | Anders Lunde         | - S. Dymecki, J. Glover, A. Lunde, B. Okaty<br>
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| B22    | 22    | Bartul Mimica        | - B. Dunn, B. Mimica, J. Whitlock<br>
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| B23    | 23    | Eike D. Schomburg    | - E. D. Schomburg, P. Dibaj, H. Nagel, H. Steffens<br>
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| B24    | 24    | Elham Jalalvand      | - E. Jalalvand, L. Wang, B. Robertson, P. Wallén, S. Grillner<br>
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| B26    | 26    | Jianren Song         | - J. Song, A. El Manira<br>
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| B27    | 27    | Jovana Belić         | - J.J. Belić, A. Kumar, J.H. Kotaleski<br>
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| B28    | 28    | Juan Pérez-Fernández | - J. Pérez-Fernández, A. Kardamakis, D.G. Suzuki, B. Robertson, S. Grillner<br>
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| B29    | 29    | Karoline Hovde       | - K. Hovde, H. Kleven, M.P. Witter, J.R. Whitlock<br>
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| B30    | 30    | Konstantina Kilteni  | - K. Kilteni, B. Andersson, H. Ehrsson<br>
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| C1     | 1     | Shreyas Mysore Suryanarayana | - S. Grillner, S. M. Suryanarayana, J. Pérez-Fernández, B. Robertson, P. Wallén  
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| C3     | 3     | Vladimir Lyalka | - V.F Lyalka, P.V. Zelenin, L-J. Hsu, G.N. Orlovsky, T.G. Deliagina  
*Changes in activity of spinal postural networks at different time points after spinalization* | Thursday June 8 - 1545-1745 |
| C4     | 4     | Wiktor Phillips | - W. Phillips, C. Del Negro, J. Rekling  
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| C5     | 5     | Amaia Nazabal | - A. Nazabal, D. Forsberg, A. Mendiguren, J. Pineda, E. Herlenius  
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<td>Nicholas Hagger-Vaughan</td>
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<td>Rodrigo Restrepo Fernández</td>
<td>Hydrogen sulfide plays an anti-inflammatory role during systemic inflammation up-regulating hypothalamus p-Akt and plasma IL-4</td>
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<td>Sebastian Illes</td>
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COGNITION

A1: Simulating deep sleep and awake states in a mammalian thalamocortical model
- AS. Nilsen, R. Murphy, BE. Juel, HE. Plesser, S. Hill, T. Nieus, M. Massimini, JF. Storm

Presenter: Andre Sevenius Nilsen - University of Oslo
Theme: Cognition
Posterboard number: 1
Time of presentation: Wednesday June 7 - 1430-1630

Authors
André Sevenius Nilsen, Ricardo Murphy, Bjørn E. Juel, Hans E. Plesser, Sean Hill, Thierry Nieus, Marcello Massimini, Johan F. Storm.

Recently, several promising measures of consciousness have been developed and tested, with high accuracy in separating conscious and unconscious states (Casali et al., 2013; King et al., 2013; Koch, Massimini, Boly, & Tononi, 2016). However, the neural mechanisms underlying changes in conscious states are not well understood. We reproduced with The Neural Simulation Tool (NEST) a computational corticothalamic model originally developed in the neural simulator Synthesis by Hill & Tononi (2005), which has functional states similar to deep sleep and awake states in the mammalian brain. These simulated states can be used to investigate the neural properties necessary for similar conscious states in the human brain. We have reproduced the model with similar functional and structural properties, thereby validating the original findings, as well as providing a foundation for implementing in silico several promising metrics of consciousness based on electrophysiology. In conjunction with electrophysiological experiments on humans and mice we will use the model to investigate and test theories of consciousness such as Integrated Information Theory (Oizumi, Albantakis, & Tononi, 2014) and the Global Neuronal Workspace Theory (Dehaene, Charles, King, & Marti, 2014).

References


A2: Speed coding in fast-spiking interneurons of the medial entorhinal cortex  
- J. Ye, A. Nagelhus, S.-J. Zhang, E. Kropff, M.-B. Moser, E. Moser

Presenter: Anne Nagelhus - Norwegian University of Science and Technology
Theme: Cognition
Posterboard number: 2
Time of presentation: Wednesday June 7 - 1430-1630

J. YE1, A. NAGELHUS1, S.-J. ZHANG1, 2, E. KROPFF1, 3, M.-B. MOSE1, E. MOSER1

1. Kavli Institute for Systems Neuroscience and Centre for Neural Computation, NTNU, Trondheim, Norway
2. SZU-CUHKSZ Joint Research Centre for Artificial Intelligence and Brain Engineering, Shenzhen University, Shenzhen, China
3. Leloir Institute, IBBA-CONICET, Buenos Aires, Argentina

The medial entorhinal cortex (MEC) is the hub of a spatial representation system consisting of a variety of functional cell types, including grid cells, border cells and head direction cells, which each represent a specific element of the animal’s current location. For activity to be translated from one group of active cells to another in a way that reflects the animal’s movement in the environment, these cells must have access to information about the current speed of the animal. Speed-responsive cells have recently been shown to exist in the MEC circuit (Kropff et al., 2015). Here we show that more than half of the entorhinal speed-cell population has interneuron-like firing properties, such as narrow waveforms and high firing rates. Around 60% of all fast-spiking cells were speed modulated, as was more than one-third of the hippocampus-projecting fast-spiking cells. Using transgenic mice with Cre expressed in neurons positive for parvalbumin (PV) or somatostatin (SST), in combination with local entorhinal injections of channelrhodopsin (ChR2)-expressing Cre-dependent adeno-associated virus (AAV), we are currently investigating the molecular identity of the fast-spiking speed cells. Since a large portion of PV-positive cells, but not SST-positive cells, in MEC layer II/III project to the hippocampus, we hypothesise that PV-positive interneurons are largely speed-modulated whereas SST-positive interneurons are not.
Principal neurons constitute the largest neuron population in the entorhinal cortex, as in most other areas of the brain. However, interneurons (INs) play an important role in information processing in all brain areas. We have investigated whether distinct subsets of INs receive specific extrinsic or local inputs, and whether there are differences within the networks of INs in the two subdivisions of the entorhinal cortex, the lateral (LEC) and medial entorhinal cortex (MEC). Using a monosynaptic tracing system with a modified rabies virus, we investigated inputs to specific interneuron groups in LEC and MEC. Parvalbumin (PV) cells are the most numerous IN subgroup, making up approximately 50% of the total IN population. PV cells in MEC receive the majority of their inputs from the hippocampal and parahippocampal regions, whereas LEC PV cells get their main input from the neocortex, piriform cortex and subcortical areas. This input pattern closely resembles the total input to the entorhinal subdivisions described in classical tracer studies (Burwell & Amaral, 1998). Interestingly, when looking at the intrinsic connections of PV cells in the two subdivisions this seemed different. PV-cells in MEC received a substantially smaller percentage of their inputs from the local network compared to PV-cells in LEC. When investigating the connections of somatostatin cells, another major interneuron subgroup, we saw similar results. This indicates that INs in EC receive external inputs that are similar to those received by the total cell population. However, the local connectivity across the two subdivisions could be different.
A4: Higher intraindividual variability is predicted by poorer cognitive control and not an ADHD diagnosis in a cognitively high-functioning sample of adults

- D.A. Jensen, L. Sørensen, D. Wollschläger, A. Halmøy, J. Haavik, A.J. Lundervold

Presenter: Daniel André Jensen - University of Bergen

Theme: Cognition

Posterboard number: 4

Time of presentation: Wednesday June 7 - 1430-1630

Background: Increased intraindividual variability (IIV) has been repeatedly associated with ADHD and considered an etiologically important factor for the disorder. However, it has also been described as a transdiagnostic marker for general psychopathology, and has in normal aging been assumed to be associated with reduced cognitive control. Recent findings from a study of children with ADHD indicate that increased IIV is secondary to working memory (WM) deficits. Based on these findings we aimed at investigating whether IIV, measured using an ex-Gaussian approach, would differentiate between a group of cognitively high-functioning adults with ADHD and a group of healthy controls (HC), or whether differences in IIV would be more closely associated with scores on a WM-measure, independently of ADHD.

Methods: 28 adults with ADHD and 28 HCs completed the Stop Signal Task, generating reaction time measures, as well as the Paced Auditory Serial Addition Test and the Color-Word Interference Task (CWIT) to obtain measures of WM and a combination of inhibition and switching, respectively. Results: The groups did not differ on measures of IIV or WM, but analyses showed a significant difference in IIV between participants scoring in the lowest and highest quartiles on WM ($p = .011$). The correlation between IIV and both the WM and CWIT scores were significant ($ps < .01$) across the entire sample.

Conclusion: The findings provide preliminary support for the notion that IIV in adult ADHD is secondary to reduced WM, and a strong association between increased IIV and reduced cognitive control.
Dominika Radziun, Henrik Ehrsson

The perception of one’s own body in space depends on the dynamic integration of signals from the different sensory modalities. Earlier studies have shown that visual, tactile and proprioceptive information contributes to this process. However, little is known about the possible role of auditory cues in the multisensory integration of bodily signals. To address this issue we studied the effect of auditory feedback in the somatic rubber hand illusion. The classic version of this illusion is elicited by repeatedly moving the blindfolded participant’s left index finger so that it touches a right rubber hand, whilst synchronously touching the participant’s real right hand. After approximately 10s of such stimulation, most participants experience an illusion of touching their own hand. We created four conditions and tested 30 healthy participants: (1) synchronous touches without auditory cues (classic illusion); (2) asynchronous touches without auditory cues (control); (3) synchronous touches with *synchronous auditory cues*; (4) synchronous touches with *asynchronous auditory cues*. The questionnaire results showed that the illusion was elicited in all condition with synchronous touches. Importantly, we observed significantly greater proprioceptive drift towards the rubber hand in the synchronous auditory condition compared to both the asynchronous auditory condition (p = 0.0075) and the condition with synchronous touches without auditory feedback (p = 0.0225). These results demonstrate that auditory cues modulate the somatic rubber-hand illusion. This suggests that auditory information is used in the formation the coherent multisensory representation of one’s own body.
Entorhinal cortex constitutes the main gateway for information entering the hippocampal formation. Projections to the hippocampal subfields dentate gyrus and CA2/CA3 originate mainly from reelin immunoreactive cells in layer II of both entorhinal subdivisions, the lateral and medial entorhinal cortex (LEC and MEC, respectively). Reelin immunoreactive stellate cells in MEC layer II communicate with each other almost exclusively through fast-spiking (FS) inhibitory interneurons (Couey et al., 2013; Pastoll et al., 2013), but little is known about the local circuit organization of principal cells in layer II of LEC.

In this study, we sought to explore the local microcircuit of principal cells in layer II of LEC. We carried out simultaneous whole-cell recordings in vitro of clusters of up to four neurons in LEC layer II, aiming to record from fan cells. Most recorded clusters contained a mix of all principal cell types, however, fan cells were most abundant. Among 98 pairs of morphologically recovered fan cells, excitatory connections were observed in three pairs. In contrast, six inhibitory connections were detected in the same data set, likely due to activation of an intermediate interneuron. Subsequent recordings from clusters of fan cells and interneurons showed stronger inhibitory input to fan cells from FS interneurons compared to non-fast spiking interneurons. Our data point to sparse monosynaptic connectivity between fan cells and further suggest an important role for FS interneurons in the fan cell microcircuit. Whether a similar microcircuit organization also applies to the other principal cell types in layer II is not clear.
Human and animal studies indicate the importance of prefrontal cortex (PFC) in cognitive processes, including attention and working memory. In earlier work, mice were trained in an attention-demanding goal-directed task, the 3-choice serial reaction time task. In the task the animals are required to report the location of a visual cue, and the responses are classified as correct, incorrect or omitted. Neurons in medial PFC were recorded extracellularly, and wide spiking putative pyramidal neurons (PC) and fast-spiking inhibitory parvalbumin (PV) expressing interneurons were identified. The firing of PV-interneurons were statistically different during attentional processing in correct and incorrect trials. Optogenetic suppression and 40 Hz drive of PV-interneuron activity were found to reduce and enhance behavioural performance, respectively (Kim et al. Cell 2016). In the current project we have analysed the firing patterns in terms of degree of rhythmicity in firing (oscillation score), variation in firing frequency and variation in spikes per bin. Preliminary result on all three measures confirm a statistical difference between correct and incorrect trials during attentional processing. Given these differences, population average frequency histogram and mean frequency over time are however quite similar. We are therefore applying temporal pattern detection methods in attempts to identify potential spike pattern differences. Moreover, we are testing a hypothesis based on computational modelling using so called Bump attractor networks. In particular, given the experimental evidence for the importance of PV-interneuron activity, we are investigating the differences in PV-interneuron activity in correct and incorrect trials as predicted by the model.
F. Palumbo, R. Pelgrims, E. Yaksi

Understanding the interactions between cortical and limbic brain regions is the key for understanding how animals build a mental map of their environment and generate/store memories in highly interconnected circuits of the brain. One key strategy for studying these computations is to monitor the activity of the entire cortico-limbic assembly of the brain and record the activity of thousands of individual neurons simultaneously, in large scale and with sufficient detail. The small and transparent brain of a small vertebrate, the zebrafish, provides a feasible solution to the problem of combining “scale” and “detail” to investigate neural activity.

Despite the common public belief, the fish are able to perform well in challenging cognitive tasks and exhibit learned behaviours. It is however less clear whether larval zebrafish can perform such complex cognitive tasks. In order to study whether and how larval zebrafish can perform classical learning, we developed a fully automated, medium-throughput conditioned place avoidance task, where up to 6 freely behaving zebrafish larvae can interact with their environment in a closed loop configuration. We showed that starting from 1 week post fertilization zebrafish larvae can very quickly learn to avoid distinct zones of the behavioral arena marked by visual cues. We also showed that the animal performance increases across development. We are now investigating temporal aspects of these learned behaviors and testing the long-term retention of these memories. Our ultimate goal is to study the changes in brain connectivity associated with learning in the zebrafish homologues of the hippocampus and amygdala.
In order to successfully interact with our dynamic environment, we need to make an accurate estimation of what is up, down, left and right from us, also referred to as self-orientation perception. Self-orientation perception is a result of visual-vestibular integration. Previous research has shown that missing or ambiguous sensory information (e.g. when the visual input is altered), can lead to a paradoxical feeling of ‘being upside down’ – also known as ‘inversion illusion’. The aim of the present research project was to investigate the role of body ownership on self-orientation perception. More specifically, we proposed that ownership might affect the weighting of visual-vestibular information and thus influence perception of self-orientation. Body ownership was manipulated using synchronous and asynchronous visual-tactile stimulation of a body seen from first-person perspective by means of virtual reality. Meanwhile, the visual scene, a fully furnished room, was rotated slowly around the roll axis. At a 180° stop, participants had to judge the appearance of a ‘shaded disk’ stimulus. Shaded disk stimuli are perceived as 3-dimensional spheres and, as light is assumed to come from above, the perception of a shaded disk depends on subjectively perceived self-orientation. Results showed that illusory ownership affected the 3-dimensional interpretation of the shaded disk stimuli and hence caused a reweighting of visual-vestibular input. Visual cues overruled the gravitational forces detected by the vestibular system, resulting in an experience of an inversion illusion. The results indicate that body ownership is necessary for our perception.
Hippocampal electrophysiological oscillations, namely theta and ripples, have been implicated in encoding and consolidation of new memories, respectively. According to existing literature, hippocampal dentate spikes are prominent, short-duration (< 30 ms), large-amplitude (~2-4 mV) fluctuations in hilar local-field potentials that take place during awake immobility and sleep. Interestingly, previous studies indicate that during dentate spikes dentate gyrus granule cells increase their firing while firing of CA1 pyramidal cells are suppressed, thus resulting in momentary uncoupling of the two hippocampal subregions. To date, the behavioral significance of dentate spikes is unknown. Here, to study the possible role of dentate spikes in learning, we trained adult male Sprague-Dawley rats in trace eyelink classical conditioning. For one hour immediately following each conditioning session, one group of animals received hippocampal stimulation via the ventral hippocampal commissura (vHC) contingent on dentate spikes to disrupt the uncoupling between the dentate gyrus and the CA1 subregions. A yoked control group was stimulated during immobility, irrespective of brain state, and another control group was not stimulated at all. As a result, learning was impaired only in the group where vHC stimulation was administered contingent on dentate spikes. Our results suggest dentate spikes and/or the associated uncoupling of the dentate gyrus and the CA1 play a significant role in memory consolidation. Dentate spikes could possibly reflect reactivation and refinement of a memory trace within the dentate gyrus triggered by input from the entorhinal cortex.
Recent interest in consciousness has created a surge in research trying to objectively assess levels and states of consciousness. However, little is known about whether psychedelic states, with their altered phenomenology, affect putative measures of levels of consciousness.

Perturbational complexity index (PCI) is a theoretically based index of consciousness determined by perturbing cortical activity with transcranial magnetic stimulation (TMS) and calculating the algorithmic complexity of the spatiotemporal dynamics of the electroencephalographic (EEG) response. PCI has been used to assess levels of consciousness across different states and patient groups. Fully conscious states such as wakefulness give high PCI values, whereas deep sleep, anaesthesia, and other unconscious states give low PCI (Casali et al., 2013).

Anaesthetic doses of ketamine produce behavioural unresponsiveness, accompanied with vivid dreams, and is associated with high PCI scores similar to wakefulness (Sarasso et al., 2015). Since sub-anaesthetic doses of ketamine give a qualitatively changed, psychedelic state of wakefulness without changing the physiological level of arousal, we wanted to test, for the first time, whether PCI changes in this condition compared to normal wakefulness.

Using sub-anaesthetic doses of ketamine in ten healthy participants, we measured PCI by TMS and high-density EEG in parietal and premotor cortices, before, during, and after ketamine administration. We found no significant changes in PCI scores induced by ketamine, even when controlling for the intensity of the psychedelic experience. These results contribute to the discussion of how levels and contents of consciousness are related. Additional methodological and experimental issues will be discussed.


The hippocampus receives inputs from a variety of spatially modulated cells in the medial entorhinal cortex, including grid, border and head direction cells. These inputs are thought to be integrated by individual hippocampal cells and influence the properties of their place fields, which represent an animal’s specific location in space. In particular, it has been hypothesised that these spatially localised firing patterns can be achieved by integrating inputs from grid cells of different modules. However, which entorhinal cortical cell type(s) and grid cell modules are involved in the formation of a single cell’s place field remains unclear.

We are developing a method that utilises a developmental approach to achieve extreme virus dilutions. This enables us to target a single cell in the CA3-subfield of the hippocampus with a pseudotyped and G-protein deleted rabies virus expressing Channelrhodopsin-2 (ChR2). The retrograde, monosynaptic transfer of the virus from this single cell will allow us to detect its inputs in layer 2 of the medial entorhinal cortex. Using electrophysiology and light-mediated activation of ChR2 we can thus identify the spatial properties of these input cells while the animal is exploring an open field environment.

We present preliminary data showing that targeting a large group of cells in CA3 with this method allows us to identify spatially modulated cells, including grid and aperiodic spatial cells, which provide direct, monosynaptic input to the hippocampus. Hence, these proof-of-concept results demonstrate the potential of using this method to functionally identify the inputs to a single cell in vivo.
GABAergic interneurons in the hippocampus form a highly diverse group with 25 identified cell types only in the CA1 hippocampal region. The oriens lacunosum-moleculare (OLM) cell plays an important role in gating the information flow received from the internal (CA3) and external (entorhinal cortex) inputs to CA1 pyramidal cells. We have previously shown that a subpopulation of OLM cells express the nicotinic acetylcholine receptor α2 subunit (Chrna2), so called OLMα2 cells. Previous studies suggest that dorsal and ventral hippocampus exert cognition and emotion-related functions, respectively. We will attempt to further investigate this hypothesis and the underlying hippocampal circuitry. We found that excitation of OLMα2 cells in the intermediate hippocampus resulted in impaired novel object recognition. Further, activation of ventral OLMα2 cells had an anxiolytic effect in an innate anxiety predator odor task. Our observations also revealed that OLMα2 cells are the driving force of cholinergic-dependent, so called type 2 theta oscillations, which seem to propagate from ventral to dorsal hippocampus. Our ongoing work attempts to answer how the observed phenotypes are reflected in the local field potential activity (LFP), both locally and in the interaction with hippocampus-associated structures. To answer this question, we are recording LFP along the dorso-ventral hippocampal axis, prefrontal cortex and amygdala during the behavioral paradigms mentioned above. Potential circuit mechanisms underlying the observed behaviors, both intra- and inter-structural, will be discussed.
Attention allows us to filter out irrelevant information in favor of relevant information. The medial prefrontal cortex (mPFC) has been demonstrated as central to the control of attention, and directly influences sensory processing. The cellular and physiological underpinnings are yet to be characterized, including the action of subcortical neuromodulators. We could recently show that local fast-spiking inhibitory interneurons expressing parvalbumin (FS-PV) directly contributes to mPFC’s control of attention (Kim et. al. 2016). The firing of mPFC FS-PV neurons correlates to the level of attention allocated in goal-directed behavior, and mPFC FS-PV neurons synchronize the activity of local populations of excitatory neurons during successful attentional processing. Generation of cortical gamma oscillations has been linked to the activity of inhibitory long-range input from the basal forebrain (BF). Moreover, the PFC is a key site for cholinergic mediation of both attentional control processes and cue detection, and disruption of cholinergic transmission is associated with impaired attention in a variety of neuropsychiatric disorders, including ADHD and schizophrenia.

We have traced the monosynaptic input from the BF to four different cell types in the mPFC, creating a complete anatomical map of the circuit. We are currently performing functional investigations of several cell-types in the BF giving input to PFC. Using optogenetics in mice performing a demanding attention task we are investigating the role of cholinergic and long-range PV neurons in the BF, respectively, in mPFC control of attention. As a next step we will combine the optogenetic manipulations with recordings of mPFC activities during attention.
A15: Postrhinal projections to the parahippocampal region in the rat
- T. Doan, MP. Witter

Presenter: Thanh Doan - Norwegian University of Science and Technology
Theme: Cognition
Posterboard number: 15
Time of presentation: Wednesday June 7 - 1430-1630

The rodent postrhinal cortex (POR), homologous to the primate parahippocampal cortex, provides the major visual and visuospatial input to the parahippocampal region (PHR) and hippocampal formation. It is involved in contextual information processing, likely by monitoring and signaling changes in the spatial environment. Several studies have attempted to describe the projections of the POR to the PHR but a detailed comprehensive description is still lacking.

The present study examined the topographical and laminar organization of POR projections to the PHR in the rat with the use of anterograde tracers, Phaseolus vulgaris-leucoagglutinin, biotinylated dextran amine and conjugated dextran amine.

Our results corroborated previous findings demonstrating an extensive intrinsic connectivity in POR and dense projections to the medial entorhinal cortex (MEC). We found that the dorsal part of POR projects to ventral MEC and that the ventral part of POR projects to dorsal MEC. Our experiments also revealed substantial POR projections to the perirhinal cortex (PER) and lateral entorhinal cortex (LEC) building upon previous findings (Burwell and Amaral 1998). This challenges the current concept of parallel input pathways to the hippocampal memory system mediated by distinct PER-LEC and POR-MEC streams, and suggests a more complex role of POR in the PHR.

A whole-brain atlas of inputs to inhibitory and excitatory neurons in prefrontal cortex
- Y. Xuan, S. Ährlund-Richter, D. Fürth, K. Meletis, M. Carlén

Presenter: Yang Xuan - Karolinska Institutet
Theme: Cognition
Posterboard number: 16
Time of presentation: Wednesday June 7 - 1430-1630

Y. XUAN, S. ÄHRLUND-RICHTER, D. FÜRTH, K. MELETIS, M. CARLÉN;
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Abstract:

The prefrontal cortex (PFC) is pivotal to cognitive and emotional processing, and changed activity in the prefrontal network is thought to underlie symptomatology in neuropsychiatric disorders and addiction. Activity in the PFC is shaped both by the balance of inhibitory and excitatory actions in the local network and by long-range input from other brain areas, including neuromodulatory systems. We map for the first time all mono-synaptic input to three central populations of inhibitory interneurons (parvalbumin, somatostatin or vasointestinal peptide expressing) and to the excitatory (calcium/calmodulin-dependent protein kinase IIα expressing) neurons, respectively, in the mPFC. For this we developed a two-vector system (one adeno-associated viral vector (AAV) and one rabies vector) for retrograde tracing of monosynaptic inputs to genetically defined populations of neurons. The AAV has been modified to enable reliable identification of starter cells. The EGFP expressing input neurons can be plotted in the 3D space onto a reference atlas using our recently developed software suit.

Our preliminary data shows that the three types of inhibitory neurons and the excitatory neurons receive a surprisingly high degree of similar inputs. The main input to both excitatory and inhibitory neurons in PFC is derived locally, but all four types also receive extensive long-range input from the rest of cortex. Sub-cortically the basal forebrain and thalamus provide the most prominent input. We are currently performing detailed analysis of the molecular characteristics of key input areas to establish how specific cell-types provide input to the mPFC circuitry.
Abstract

Precise knowledge of our limbs’ position in space is fundamental for goal directed action. The brain’s representation of our body in space is thought to come about by a process of multisensory integration of visual, tactile and proprioceptive signals. In this study we devised a new setup that allowed us to displace participant’s right hand without their subjective awareness. We accomplished this by having the participants view a live video feed of their hand. In the active condition we made use of a sensorimotor illusion that caused the participants to actively but unknowingly displace their own hand, whereas in the passive condition we displaced the participants hand slowly enough for it to go by unnoticed by the participants. We show that during active displacement, the participants are significantly worse at locating their hand’s veridical location compared to passive displacement. These results indicate that the recalibration of the hand’s spatial position differs depending on whether the hand has been displaced actively or passively. We further show that the same effect is observed when the participants see a block of wood instead of their hand in the visual location of their hand, which indicates that this effect is independent of ownership over the visual object. These results have bearing on the perceptual mechanisms of recalibration of perceived limb location.
Febrile seizures (FS) are the most widespread type of early-life seizures, which may cause temporal lobe epilepsy later in life. Hyperthermia-related hyperventilation resulting in blood and brain alkalosis has been identified as one the mechanism triggering FS. FS are characterized by limbic onset and progressive generalization. This pattern suggests spreading of the ictal activity from limbic structures to the brainstem. Whether the brain stem might act as an independent generator of FS has not been studied so far.

Precollicular brain transection was done in P13 rat pups to completely isolate the brainstem from the forebrain. Standard procedures of hyperthermia or 3 mg/kg kainic acid (KA) i.p. injection were used to provoke experimental FS and kainate seizures, respectively, in transected and sham-operated rats. Behavioral seizures were evaluated using video recording, and blood pH was measured at seizure onset.

Strikingly, in both the FS and KA model, transected rats had shorter latency to seizure onset than sham-operated animals, with more severe (i.e. tonus-clonus) initial seizures, which were not preceded by typical behaviors related to the onset of limbic seizures. FS in transected animals had a lower temperature threshold than in sham-operated, but similar blood pH.

The brainstem has a high sensitivity to standard triggers of seizures, hyperthermia and kainate, which have previously been thought to primarily act via limbic circuits. Our data further suggest that the forebrain may actively suppress brainstem seizures.
A19: Poster Retracted

Presenter:
Theme: Development
Posterboard number: 19
Time of presentation: Wednesday June 7 - 1430-1630

Poster retracted
During development interneurons (INs) are derived from the ventrally located ganglionic eminences (GE). While cortical and hippocampal INs have been shown to derive from both medial GE and caudal GE, all striatal interneuron populations so far described originate in the medial GE. In addition, while the majority of the telencephalon, including cortex and hippocampus is largely excitatory, the principal cells of the striatum (SPNs) are inhibitory. Meaning that INs with shared developmental origin integrate into functionally distinct local circuits. In order to investigate if this integration in anyway affects the molecular and electrophysiological identity of these cells, or if functional similarities of INs in these distinct circuits are reflected in their molecular profile. To address this we performed single-cell RNA sequencing in combination with whole-cell electrophysiological recordings (PatchSeq) on a wide range of telencephalic interneurons. Our results reveal that there are significant differences between Pvalb-expressing cells of the striatum and cortex. Furthermore, striatal Pvalb-expressing cells are part of a larger transcriptionally defined Pthlh-expressing population, not uniformly expressing Pvalb, exhibiting a continuum of electrophysiological properties. Our findings therefore suggest that molecular identity corresponds to, and explains functional identity. In addition, it shows that despite shared developmental origin, the integration into distinct circuits affects both the molecular as well as the electrophysiological identity of MGE derived INs.
The neuronal network of the cortex is composed of two main neuronal populations: glutamatergic projection neurons that communicate with other brain regions, and GABAergic interneurons that control the network output by modulating the activity of projection neurons. Defects in the GABAergic system are discussed to be involved in the pathogenesis of several neurological diseases, and hence, major research efforts have been devoted to the understanding of interneuron generation, migration, network integration and survival.

Cortical interneurons are generated in the ganglionic eminences, and migrate tangentially into the developing cortex where they distribute radially to settle in the correct layer, and to integrate into the local network. The final maturation of GABAergic interneurons continues well into postnatal stages.

Activin receptor-like kinase 4 (Alk4) is expressed in both glutamatergic and GABAergic neurons. As a type I receptor for several members of the TGF-beta superfamily, it signals in conjunction with activin receptor type IIB upon ligand binding.

Despite almost ubiquitous expression in the embryonic brain we find that Alk4 signaling in GABAergic precursor cells is required specifically for the development of the somatostatin and reelin expressing subtypes of interneurons. The loss of these interneurons leads to a decreased seizure threshold in the adult mouse.
A variety of ligand types signal through the p75 neurotrophin receptor (p75NTR) either alone or in complex with a number of different co-receptors. The cellular outcomes of these different ligands are diverse, and which pathway is predominant depends upon the relative availability of the different ligands and co-receptors. Expression of these proteins varies depending on tissue type and developmental stage but also in response to neuronal activity and external events.

To study the roles of specific p75NTR pathways in vivo, we generated mice carrying a point mutation in the p75NTR transmembrane domain (C259A), which reduces the response of the receptor to neurotrophins but not to myelin derived ligands, such as Nogo or MAG (Vilar et al, Neuron 2009).

Here we show that C259A mice have an increased activation of pathways downstream of myelin derived ligands and that these animals do not show the same changes in anxious and depressive behaviours observed in p75NTR null (KO) mice. Interestingly, exposure to early life stress, which alter the neurotrophin levels in the hippocampus, have differential effects upon both dendritic complexity and behaviours of wildtype, C259A and p75NTR KO mice. These results suggest a balanced interplay between the different signalling pathways mediated by p75NTR and that both external events and genetic differences can skew this balance.
The brain’s representation of space relies on an extended network of specialized cell types spanning multiple interconnected brain regions and including place cells in the hippocampus, and grid, border, head direction and speed cells in the medial entorhinal cortex. Properties of these cells are thought to reflect the intrinsic connectivity of the entorhinal-hippocampal network. However, little is known about how this extended microcircuit is assembled during development. Place, border and head direction cells exhibit adult-like features from the onset of spatial navigation at 2-3 weeks of age, while the periodic firing pattern of grid cells emerges later, at approximately 4 weeks, suggesting that early interactions between subregions of the network might be crucial for the eventual emergence of spatially specific firing.

To determine how this network is set up during early postnatal development, we monitored markers of structural maturation in developing mice, both in naïve animals and after temporally restricted pharmacogenetic silencing of specific cell populations. Our data show that the entorhinal-hippocampal circuit matures in a linear sequence that recapitulates excitatory information flow through the adult network. Entorhinal stellate cells provide an activity-dependent instructive signal that drives maturation sequentially and unidirectionally through the intrinsic circuits of the entorhinal-hippocampal network. Excitatory activity at each stage of the circuit is necessary for the development of the following stages. These findings raise the possibility that a small number of autonomously developing neuronal populations operate as intrinsic drivers of maturation across widespread regions of cortex.
A24: Role of Na⁺,K⁺ ATPase regulators FXYD6 and FXYD7 in motor neuron physiology  
- I. Allodi, J. Njissen, J.A. Benitez, G. Bonvicini, M. Cao, J. Jakobsson, E. Hedlund

Presenter: Ilary Allodi - Karolinska Institutet  
Theme: Development  
Posterboard number: 24  
Time of presentation: Wednesday June 7 - 1430-1630

Ilary Allodi1, Jik Njissen1, Julio Aguila Benitez1, Gillian Bonvicini1, Ming Cao1, Johan Jakobsson2 and Eva Hedlund1  
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The Na⁺,K⁺-ATPase isoform maintains the gradient of Na⁺ and K⁺ across the cell membrane and restores ion concentration in excitable tissues. FXYDs are a family of seven tissue specific ion transport regulators that modulate Na⁺,K⁺-ATPase activity by binding to α-NKA subunits. In the nervous system FXYD6 and FXYD7 are known to favor extracellular K⁺ removal after neuron firing and to differentially modulate the Na⁺,K⁺-ATPase affinity for K⁺, with FXYD6 increasing the affinity for K⁺ when binding α1-NKA. Our in vitro studies conducted on stem cells derived-motor neurons (MNs) and in vivo investigations in mouse tissues demonstrate that FXYD6 is highly expressed during MN development. Interestingly, while the majority of somatic MNs present in the spinal cord down-regulates FXYD6 during early postnatal stages, restricted subpopulations maintain the expression also during adulthood. Moreover, transcriptomic analysis of human tissue demonstrates that FXYD6 and FXYD7 are differentially expressed in somatic MNs and mutually exclusive during adulthood. Importantly, MNs with differential vulnerability to degeneration in amyotrophic lateral sclerosis (ALS) express these two isoforms at different levels; FXYD6 is found in slow-twitch spinal MNs and oculomotor neurons which are relatively resistant, while FXYD7 is preferential to vulnerable spinal MNs. Further studies revealed that autonomic MNs present in the intermediolateral nucleus (IML) of the spinal cord, also resistant in ALS, show high FXYD6 protein levels. Since differential regulation of the isoform could potentially affect MN homeostasis and survival, FXYD6 and FXYD7 could become potential targets to further clarify MN differential vulnerability.
Perineuronal nets (PNNs) are a specialized form of extracellular matrix in the CNS that mainly enwraps parvalbumin (PV) expressing inhibitory interneurons. They assemble in parallel with the maturation of the inhibitory network and closure of critical period plasticity. Several lines of evidence support a role for PNNs in limiting adult brain plasticity and in the pathology of some neurological disorders. While the mature PNN is a structure of several components, recent work suggests that aggrecan, a product of the ACAN gene, is vital for the PNNs. To investigate the role of aggrecan for PNN assembly and stability, and its contribution to brain plasticity, we have developed a Cre-inducible conditional ACAN knock-out mouse.

To introduce Cre to the ACAN mouse we either injected a viral vector expressing Cre recombinase under control of the synapsin promoter in adult mice, or crossed the mice with PV-Cre mice that express Cre downstream of the PV transcript.

Conditional knock-out of ACAN efficiently eliminated both aggrecan and PNNs with both approaches. Adult ACAN/PV-Cre mice were lacking PNNs in all cortical areas. Functional characterization of the mouse line is currently being conducted using different behavioral tests and in vivo electrophysiological recordings. Preliminary data suggest that ACAN knockout leads to lifelong high plasticity levels, and that animals without PNNs show reduced levels of anxiety.

Our results indicate that aggrecan is vital for the assembly and stability of PNNs, making the ACAN mouse a robust tool enabling targeted investigations to reveal the role of PNNs in plasticity and disease.
The p75 neurotrophin receptor (p75NTR) orchestrates injury responses in the nervous system. It signals through three main signaling pathways: i) JNK/cell death, ii) NF-kB and iii) RhoA. Activation of the NF-kB pathway upon NGF binding to p75NTR depends upon recruitment of the serine/threonine-protein kinase (RIP2) to the p75NTR death domain. This is thought to promote cell survival, but evidence in neuronal cells is lacking. Here we report that RIP2-p75NTR-mediated NF-kB activation is essential for survival of cerebellar granule neurons (CGN) in vivo during cerebellar development. Neurons lacking RIP2 fail to activate NF-kB pathway in response to NGF, leading to increased CGNs apoptotic activity. Loss of RIP2 induces the activation of JNK pathway by increasing recruitment of TNF-associated factor 6 (Traf6) to p75NTR. Moreover, we show that RIP2 competes with Traf6 to bind to p75NTR in a steric hindrance mechanism. Adult RIP2 mutant mice exhibit reduction in CNG numbers, increased CGN dendritic length and reduction in PC-PF synaptic markers and PC spines. Together, these findings reveal that interaction with RIP2 is crucial for p75NTR-mediated survival of CGNs and formation and maintenance of proper adult cerebellar architecture.
Lagartos-Donate MJ; Witter MP

Binding objects or events together in place and time is one of the fundamental functions for an animal to survive successfully in its environment. In mammals, the neural basis of spatial memory has been thought to largely reside in the hippocampus and parahippocampal regions. One of the relevant parahippocampal areas is the postrhinal cortex (POR), which provides spatial and contextual information from parietal and visual cortex (Furtak et al. 2007) to the hippocampus through its projection to the medial entorhinal cortex (MEC). POR provides a main excitatory input to neurons in layer II of MEC that in turn project to the dentate gyrus and CA3 of the hippocampus (Koganezawa et al. 2015)

The various types of spatially modulated neurons in MEC show a gradual postnatal emergence (Tan et al., 2016). This gradual emergence may depend on the development of main inputs and we thus studied the postnatal development of POR inputs to MEC.

By combining anterograde tracing and intracellular filling of retrogradely identified projection neurons in MEC, we studied the postnatal development of POR projections to MEC in rats. Our results showed that from P3 until P23 the density of these projections increased from dorsal to ventral, but always stayed in line with the adult topography (Furtak et al. 2007). We further used voltage dye imaging to determine the postnatal establishment of a functional connectivity. This electrophysiological approach revealed that LII/III and LV neurons of POR make functional contacts in MEC from P10-11 onwards and there is a progressive decrease in the POR network excitability between P5 and P23. The main functional changes of the POR-EC projection happens after the first half of the second postnatal week, coinciding with a developmental shift in the actions of GABA.
The laminar organization of the cerebral cortex comes about as result of sequential migration of neurons in an inside-out manner. Migration defects emerge as a common denominator in a number of developmental brain disorders, including seizures and autism, however the cellular and molecular mechanisms at play are poorly known. The qualitative maturation of GABA\(_A\)R-signaling has been proposed to act as a regulator of neuronal migration rate. The ontogenetic shift from excitatory to inhibitory GABA signaling is mediated by up-regulation of KCC2 which lowers neuronal chloride concentration. Notably, KCC2 is a multifunctional protein which modulates the actin cytoskeleton in an ion transport-independent manner. Up-regulation of KCC2-mediated Cl\(^-\) extrusion has been shown to regulate interneuron migration, but it is not known whether and in what way KCC2 affects principal neuron migration. Using constitutive (KCC2\(^{+/−}\)) knockout mice we first demonstrate that global loss of this neuron-specific protein does not perturb gross cortical lamination. Then, using in utero electroporation of cre-recombinase in conditional KCC2\(_{lox/lox}\) mice to achieve specific ablation of KCC2 in a subpopulation of migrating somatosensory cortical principal neurons, we show that loss of KCC2 results in marked acceleration in the migration rate of these cells. Strikingly, this effect was rescued both by co-electroporation together with cre of either wildtype KCC2 or an N-terminally-truncated ion transport inactive variant (KCC2-ΔNTD). As KCC2-ΔNTD is known to retain its interaction with the actin cytoskeleton, our data suggest a novel ion transport-independent role for KCC2 in controlling the migration rate of cortical principal neurons.
The entorhinal cortex (EC) is the major interface between hippocampus and neocortex. Studies in rodents suggest two parallel circuits with different set of inputs to EC, different connections to hippocampal subfields and, hence, different function of those two areas related to memory for object and context information (Witter et al., 2014). On this basis the EC of rodents is divided to medial EC (MEC) and lateral EC (LEC) areas. In humans evidence for functional division based on fMRI study exists (Maas et al., 2015). However, whether the same division of EC on histological level exists in human and is it homologous to the rodent’s has not yet been assessed for.

Current study was done on prenatal human brains of 20-26 gestational weeks from legal autopsies (approval of the Ethics Committee #00003875). During prenatal period of development common structural features of functionally similar areas exist even between representatives of a distant taxa.

We used microtubule-associated protein 2 (MAP2) and neurofilament heavy chain protein (N200) as the markers of neuronal maturation in addition to calcium-binding proteins. The MAP2-positive neurons in posterior-MEC were found only in layer I/II patches, whereas anterior-LEC MAP2-positive pyramidal cells were found in layer III. This allowed us to make 3D reconstruction of EC which reveals posterior-MEC/anterior-LEC division similar to one found by fMRI studies and homologous to MEC/LEC of rodents.

The research was supported by SPbSU grant #1.38.333.2015, and conducted with the use of SPbSU "CM&CT" Research Park facility (project #109-306).
A30: Neuronal circuit dysfunctions in the primary visual cortex of a mouse model of intellectual disability
- P. Krishnamurthy, E. Dylda, P.C. Kind, N.L. Rochefort

Presenter: Pradeep Krishnamurthy - University of Edinburgh
Theme: Development
Posterboard number: 30
Time of presentation: Wednesday June 7 - 1430-1630

Keywords: Syngap, two-photon, Cortex

Intellectual disability (ID) in humans is a neurodevelopmental disorder characterized by impaired intellectual and adaptive functioning with a world-wide prevalence of about 2-3%. One common cause of ID is associated with mutations on the Syngap1 gene that encodes Synaptic GTPase activating proteins (SynGAP). These post-synaptic proteins are enriched at the postsynaptic density of excitatory synapses and transduces NMDA receptor activation to downstream pathways. A mouse model of this single-gene mutation pathology, (heterozygous Syngap knockout mice ($Syngap^{+/−}$)), has been shown to exhibit a range of behavioural and physiological impairments during development and adulthood, compared to wild type (Wt) littermates. Although synaptic dysfunctions in Syngap +/- mice have been extensively studied at the molecular and cellular levels, little is known about neuronal circuits dysfunctions. Here we performed two-photon calcium imaging in the visual cortex of awake behaving mice to compare neuronal population activity between $Syngap^{+/−}$ mice and Wt litter mates. We imaged somatic calcium signals in layer 2/3 neurons, both in darkness and during the presentation of drifting gratings, while the animal was either running or stationary. We also investigated potential impairments in experience-dependent plasticity by using the monocular deprivation paradigm. layer 2/3 neuronal responses were compared before and after seven days of monocular occlusion in adult mice. The results of these experiments should provide a basis for understanding how Syngap1 mutations affect neuronal circuit activity in cortical sensory areas.
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Keywords: development, neurotrophic theory, neurotrophins, peripheral nervous system, neuronal survival

Abstract
Naturally occurring cell death plays an important role in the construction of a functional nervous system. In vertebrate, the neurotrophic theory explains how death of neurons is regulated during this developmental period, proposing that neurons compete for limited amounts of target-derived neurotrophic signals and that the selection of the surviving neurons is stochastic, implying a similar potential for neurons to compete. Here, examining TrkC positive proprioceptive sensory neurons (PSNs), we show that before cell death they exhibit different molecular signatures that are intrinsically regulated, independent of the target and of neurotrophin signaling. We also provided direct evidence in vitro and in vivo that this heterogeneous molecular feature in PSNs is predictive of their survival during the cell death period. Thus, contrary to the prevailing model, our data suggest a selection model in which neighboring neurons with intrinsic differential fitness compete for neurotrophins in the target tissue, resulting in the elimination of cells with lower capacity to survive.
Prader-Willi syndrome (PWS) is a genetic neurodevelopmental disorder caused by a loss of paternal expression of several genes of the 15q11-q13 region, including NECDIN. Breathing perturbations, sleep apnea and blunted response to hypercapnia appear in PWS patients earlier than other symptoms. Mice deficient for Necdin (Ndn-KO) present respiratory disruptions and early dysfunctions of the serotonergic (5-HT) system similar to PWS suggesting the involvement of a serotonopathy in respiratory dysfunction. Thus, 5-HT modulatory effects on respiration in Ndn-KO mice are of practical interest. We demonstrated that Necdin is expressed in the beginning of the serotonergic system lineage; lack of Necdin resulted in defect migration of 5-HT neurons and altered 5-HT neuroarchitecture, with a prenatal loss of 5-HT neurons. Neonate Ndn-KO mice show dystrophy in serotoninergic fibers, with enlarged varicosities associated with an increase of spontaneous firing. These findings correlate with an increase in 5-HT reuptake activity and an increase in 5-HT transporter expression. Then, we assessed the capacity of genetic abolition of SERT in Ndn-KO x SERT-KO mice as well as that of early pharmacological reuptake inhibition (fluoxetine), and a 5-HT1A agonist (8-OH-DPAT) to rescue the respiratory deficits. We have demonstrated in neonatal "en bloc" preparation that both fluoxetine and 8-OH-DPAT restore the inspiratory response to hypercapnia, while the genetic ablation of SERT or fluoxetine administration in neonate Ndn-KO mice reduce the number of apneas and normalize the chemosensitivity. These results contribute to understanding of origin of the blunted hypercapnic ventilatory response in PWS patients.
The striatum is the main input structure of the basal ganglia, a series of subcortical nuclei that play a key role in motor control. Two distinct basal ganglia circuits, the direct and the indirect pathways, originate from the striatal projection neurons and are canonically believed to respectively facilitate and oppose motor behavior. Ablation studies have revealed that distinct striatal compartments have different functions in the regulation of movement, yet their role is still unclear. In order to acquire a deeper understanding of striatal compartmentalization and to validate the contextual function of the basal ganglia circuits, we aimed at selectively modulate the activity of direct pathway-medium spiny neurons in the dorsomedial striatum. This specificity was achieved by viral-genetic tools combining the dopamine D1 receptor-Cre recombinase mouse strain and the Designer Receptors Exclusively Activated by Designer Drugs (DREADDs). Our chemogenetic approach allowed remote control of signal transduction in selective neurons and, therefore, modulation of specific neuronal pathways in a temporal fashion. Here, we show that activation of inhibitory (Gαi-associated) DREADDs in dorsomedial striatal neurons attenuated locomotor activity in the open field test. DREADD-mediated inhibition was also able to reduce movement following acute cocaine administration. To validate the involvement of Gi-protein signaling pathway upon DREADD activation, we analyzed downstream effectors via immunoblotting. Moreover, immunohistochemistry confirmed that DREADD expression in the striatum was restricted to the dorsomedial region and showed both somatic and axonal/dendritic localization. Overall, our results provide further evidence supporting the role of the direct-pathway in promoting movement.
Sensory-based decisions for locomotion and gaze-shift involve the interaction of subcortical and cortical circuits. The optic tectum (superior colliculus in mammals) is central for multisensory integration and sensorimotor decision-making, regarding both orienting towards an object and conversely avoiding a collision with an object. We have investigated these reactions in an isolated eye-brain preparation with the spinal cord intact (Kardamakis et al 2015, 2016), enabling us to simultaneously monitor neural responses from different regions (e.g., the optic nerve, optic tectum and ventral roots), while delivering various types of visual stimuli ranging from dots, bars and looming (objects increasing in size dynamically) in a computer-controlled environment.

By monitoring bilateral neural activity in the ventral roots in the rostral spinal cord and deep layer tectal activity, we could identify two distinct motor response patterns selective to the specific type of visual stimuli applied. Fast looming (threatening) stimuli and vertical bars tend to induce a response preferentially in the ipsilateral ventral root. This would correspond to fictive evasion. Looming stimuli that instead slowly increase in size will evoke activity in the contralateral ventral root corresponding to orienting movements.

This selectivity was abolished when we removed the action of the local inhibitory system and/or disrupted glutamatergic synaptic transmission by local injection of gabazine or glutamate antagonists. We controlled the effect of tectal activation and inactivation by recording extracellular activity during the visual stimulus presentation as a measure to determine the causal role of tectum in visual decision-making.
The subiculum is one of the main output regions of the hippocampal formation. Together with CA1 it provides input to a number of cortical and subcortical regions which rely on spatial and mnemonic information. While the firing properties of CA1 place cells have been investigated extensively, our current knowledge of neuronal computation in the subiculum remains very limited. In previous studies of subicular neurons, Lever et al. (2009) have identified boundary vector cells and Deadwyler and Hampson (2004) have reported the presence of cells with task phase specific firing in a delayed non-match to place task. However, it is unclear how these cells are distributed in the subiculum and whether they form distinct functional populations or a single population with mixed selectivity. To address these questions, we performed extracellular recordings of single units in the subiculum while rats were alternating between random foraging for chocolate milk rewards and goal directed running in an open arena. The recorded cells where responsive to features of the environment, like the food wells or the walls, and they were differentially modulated by head direction and running speed. The different types of modulation where unequally distributed along the proximodistal axis; while cells that responded to the food wells could only be found in the very proximal part of subiculum (and the distal CA1), the others were more dispersed. It thus appears that the subicular output varies quite substantially along its proximodistal axis and that the information provided is not amplifying but complementing hippocampal CA1 output.
A36: Genetic inactivation of GFRα1 in the medial habenula of adult mice results in altered anxiety and fear related behavioral responses
- D. Fernandez-Suarez, C.F. Ibanez

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Abstract: The septohabenular pathway is composed by two tightly interconnected structures, the posterior septum and the medial habenula (mHb). These structures constitute a key linkage between the limbic forebrain and the midbrain and disruption of this pathway leads to alterations in emotional behaviours, specifically in anxiety and fear. GFRα1, a GPI-anchored receptor for GDNF (glial cell line-derived neurotrophic factor), is expressed in several brain areas such as hippocampus, septum and midbrain. In the adult brain, GFRα1 expression is highest in the medial habenular nucleus (mHb). However, the role of GFRα1 for the function of the septohabenular pathway is unknown. In this study, we showed that mice with inactivated gfra1 expression at adult stages present decreased anxiety and increased responses in fear-based learning paradigms. These results suggest that GFRα1 is required for the correct function of the septohabenular pathway in the adult brain under physiological conditions.

Key words: Anxiety, fear, habenula, septum, GFRα1, GDNF
Lesion studies have revealed that the medial amygdala (MeA) is involved in sexual behavior in male rats. However, these studies could not distinguish between neuronal cell types or target specific projections. Here, we investigated the role of glutamatergic MeA neurons, and their specific projections to the preoptic area (POA), a brain area that is also involved in sexual behavior.

AAV5-CaMKIIα viral vector constructs coding for control, stimulatory, or inhibitory DREADDs were bilaterally injected into the MeA and a bilateral guide cannula was placed above the POA. Rats (n = 18-20 per group) were assessed for sexual incentive motivation and copulation upon systemic administration of the DREADD ligand (CNO), silencing or stimulating glutamatergic neurons originating from the MeA. The same tests were conducted after intracranial CNO infusion into the POA, which enables exclusive observation of effects of glutamatergic MeA-POA projections.

The data showed a decreased number of ejaculations and an increased ejaculation latency in the copulation test upon systemic administration of CNO, an effect found in both experimental groups. In contrast, no effect was observed on sexual motivation. Silencing or stimulating the specific MeA-POA glutamatergic projection did not affect sexual motivation and behavior.

Our study indicates that MeA glutamatergic projections are involved in ejaculation, but not in other copulatory phases. These effects are not regulated by direct, glutamatergic MeA-POA projections. The convergence of the behavioral effects of stimulating as well as silencing glutamatergic MeA projections may reflect effects through different indirect pathways. Future research should focus on unraveling these pathways.
Compared to our knowledge of the molecular mechanisms underlying memory acquisition and consolidation, far less is known about remote memory storage. Perineuronal nets (PNNs), specialized extracellular matrix structures, have been hypothesized to function as a physical framework for memory storage due to their low turnover rates and stabilization of synaptic connections (Tsien, 2013). We tested this hypothesis using adult rats trained with visual fear conditioning. Recent evidence indicate that over time, visual fear memories become dependent on the lateral secondary visual cortex (V2L). We asked if intact PNNs in V2L are required for remote visual fear memory. Local injections of the enzyme Chondroitinases ABC (chABC) was used to degrade PNNs one week before remote memory retrieval. Remarkably, memory testing showed a selective disruption of the visual fear memory. When chABC injections were targeted to the primary visual cortex, the memory was not affected. Moreover, chABC treatment one week before or one day after fear conditioning did not impact learning or recent and remote memory recall. Simultaneous recordings of local field potentials from V2L and basolateral amygdala (BLA) showed increased coherency between V2L and BLA during retrieval of the fear memory in control animals while no coherent activity was observed in the chABC treated animals with impaired retrieval. These findings indicate that PNNs in V2L are critical for remote but not recent visual fear memory. Furthermore, based on our discoveries and the inherent properties of PNNs, we propose that PNNs are essential for stabilizing the neural network responsible for proper recall.
Some, apparently healthy babies exhibit Sudden Unexpected Postnatal Collapse of newborn infants (SUPC), life-threatening or fatal events, during the first week after birth. Incidence, risk factors and mechanism are not established.

Objective: We here characterize the incidence of SUPC, possible and preventable risk factors. We hypothesize that PGE2, increased after birth, induce an attenuation of hypoxic and hypercarbic responses in the newborn, that contribute to the SUPC events.

Results: Among 263738 liveborn infants in Stockholm county 2002–2015, 111 cases of SUPC in apparently healthy infants were revealed. This incidence is fifteen times higher than reported in recent national studies. The majority of SUPC cases occurred during the first 24 postnatal hours, when the newborn was in a prone position. Eight died and 21 had subsequent Hypoxic Ischemic Encephalopathy. During the first day of life all newborns exhibit high levels of PGE2 and urinary PGEM that rapidly decrease within the first 48–72 postnatal hours. In SUPC/SUDI cases where urine or CSF was analyzed, PGE2 metabolites were increased compared to age matched controls.

Conclusions: SUPC is a risk of all newborns, associated with prone position and unsupervised Skin-to-Skin-care especially during the first 24 hours after birth, when newborns autonomic cardiorespiratory responses are attenuated by PGE2.

KEYWORDS: SUDI, Perinatal transition, PGE2.
Repeated exposure to drugs of abuse results in a progressive and long-lasting enhancement of the locomotor response, a phenomenon termed locomotor sensitization, that is thought to underlie certain aspects of drugs addiction. In mice, sensitization has been shown to correlate with enhanced predisposition to drug self-administration as well as reinstatement of extinguished self-administration. In humans, sensitization has been proposed to correspond to certain features of the drug addiction syndrome, such as compulsive drug-seeking behavior. Regardless its correlate in humans, locomotor sensitization provides a simple readout to understand the mechanisms by which drugs of abuse induce long-lasting neuronal alterations.

Activin A, a member of the transforming growth factor-β (TGF-B) super-family, signals via the serine/threonine Activin-like kinase 4 receptor (ALK4), which then phosphorylate Smad2/3 and induce translocation into the nucleus to regulate gene expression. A recent study has linked Activin signaling with cocaine-induced plasticity; however, the role of Activin A and its receptor ALK4 in the context of drug abuse has not been explored.

In our studies, we found that genetic ablation of ALK4 in medium spiny neurons of the striatum blocked the expression of locomotor sensitization to cocaine as evaluated with the Two-Injection Protocol of Sensitization. Moreover, we found that viral-induced deletion of ALK4 in adult mice nucleus accumbens is sufficient to affect sensitization to cocaine. These results demonstrate that ALK4 is crucial in the development and/or expression of behavioral sensitization and suggest that Activin/ALK4 signaling plays an important role in the long-lasting plasticity induced by cocaine.
In vertebrates, serotonin (5HT) modulates aggressivity, aversive learning and impulsivity and has been implicated in anxiety and depressive-like disorders. Most of the serotonin in the vertebrate brain is released by the small and evolutionary conserved raphe nuclei, which are broadly innervating cortical and limbic areas. However, the neurotransmitter identity and downstream projection pattern of individual 5HT raphe neurons remain unclear due to their deep location in the rodent brain. In this study, we take advantage of the small and optically accessible zebrafish brain to investigate the organization of the conserved 5HT system.

To identify the neurotransmitter identity of zebrafish raphe neurons, we analyzed the co-expression of a 5HT neuron marker (tryptophan hydroxylase, Tph2) and of glutamatergic and GABAergic neurons markers (vesicular glutamate transporter 2a and glutamate decarboxylase, respectively) using confocal microscopy in transgenic zebrafish aged 1, 2 and 3 weeks. At all developmental stages, we found that none of the Tph2 neurons co-express the glutamatergic marker. However, only a subset of Tph2 positive neurons co-expresses the GABAergic marker. To identify the projection pattern of 5HT neurons, we are currently labeling individual Tph2 neurons using electroporation of dextran-coupled fluorescent dyes and tracing their axonal projections in the whole brain. This will enable us to establish whether 5HT neurons modulate the activity of all downstream targets or alternatively of one or two discrete brain regions.

Altogether, this comparative approach will enable us to better understand the structure and function of the elusive 5HT system in vertebrates.
Human genetic studies have identified numerous genetic alterations associated with autism spectrum disorder (ASD). Many of these genes are linked to pathways regulating synaptic function, including synaptic adhesion molecules such as neuroligins and neurexins. Gene products that regulate mRNA translation constitute a second group of ASD-associated genes, and altered translational homeostasis at the synapse has been highlighted as a common disease mechanism in some monogenetic and syndromic forms of ASD. However, most autism-associated mutations do not directly impact translation, and it is unknown if pharmacological strategies targeting protein synthesis are more broadly applicable in neurodevelopmental disorders. We here show that an autism-associated mutation in the synaptic adhesion molecule neuroligin-3 (Nlgn3) results in altered mTORC1-dependent signaling and reduced eIF4F assembly in mice. We have investigated the therapeutic potential of MAP-kinase interacting kinases (Mnk1/2) inhibitors in Nlgn3KO mice. Mnk1/2 modulates translation via phosphorylation of eIF4E and additional targets. Administration of Mnk1/2 inhibitors in Nlgn3KO mice alleviates some of the autism-associated behavioural phenotypes. This work highlights Mnk inhibitors as a potential treatment strategy for brain disorders with perturbed translation homeostasis.
Attention plays a crucial role in our ability to organize thoughts and actions in meaningful behavior. On a neurophysiological level, attention biases processing of certain neural representations at the expense of others. As a result, behaviorally relevant information is amplified, while distracting or irrelevant information is suppressed. The prefrontal cortex (PFC) directly influences attentional processing and the local computations underlying PFC’s control of attention are under intense investigation. Using chronic recordings and optogenetics in mice, we could recently show that fast-spiking parvalbumin (FS-PV) interneurons in medial prefrontal cortex (mPFC) are central to PFC control of attention. By strong, successful allocation of attention was characterized by strong synchronization of FS-PV neurons, increased gamma oscillations, and phase locking of pyramidal firing. Phase-locked pyramidal neurons showed gamma phase-dependent rate modulation during successful attentional processing.

The behavioural task utilized in this study, the 3-CRTT, in combination with electrophysiological recordings also allows for investigation of network activities not directly related to attention. Using the recording data collected in the earlier study we have analysed how FS-PV interneurons and excitatory mPFC neurons are modulated by impulsivity and reward anticipation/consumption.

In has recently been proposed that working memory is linked to bursts of gamma oscillations, and in line with this is a discrete process not coded by sustained activity as earlier thought. We are currently investigating the similarities between coding of working memory and attention in the PFC. Our present findings from the above analyses will be presented.
The critical ability to inhibit the urge, desire, or habit to perform spontaneous actions and to instead reflect upon the future allows us to predict scenarios and to receive better outcomes. Failure of inhibitory processes defines impulsivity. Impulsivity is a non-unitary construct, but the relationship between aspects of impulsivity is not understood. Impulsive action refers to the inability to delay or prevent actions related to the failure to withhold or cancel a strong behavioral tendency. Impulsive choice relates to impulsive decision-making and involves lack of planning and difficulties in delaying gratification. The central serotonergic (5-HT) system has long been functionally implicated in impulse control and reduced 5-HT levels have been connected to impulsivity in both humans and research animals.

To allow for selective targeting of serotonin neurons in rats we generated transgenic rats expressing Cre recombinase under the control of the Tph2 promoter. A fixed interval task was used to investigate impulsive action, and a time-discounting choice task for impulsive choice. Using optogenetic manipulations (ChR2 or Jaws) and real-time photometric measurements of calcium-transients in dorsal raphe nucleus 5-HT neurons we find that (1) inhibition of serotonergic DRN neurons leads to a general elevation of impulsivity. (2) Activation of serotonergic DRN neurons results in decreased impulsive action. (3) Increased activity of serotonergic DRN neurons improves impulsive choice, measured as willingness to wait for a larger later reward, while decreased activity suppresses patience. (4) DRN serotonergic neurons not only respond to waiting for a reward but also robustly to reward delivery.
Dysfunction of the opioid system has been linked to mood disorders. Various types of drugs of abuse, for example opiates and cocaine, target the opioid system.

Endogenous opioids exert their actions through opioid receptors expressed by neurons in limbic circuits. Morphine and heroin are ligands of a specific type of opioid receptor, the mu opioid receptor (MOR) that is encoded by the Oprm1 gene.

In order to study the contribution of specific neuron types in the opioid system for reward, motivation and addiction, it is essential to be able to target neurons expressing the opioid receptors using transgenic approaches in animal models. We can use the genetic identification of such MOR-expressing neurons to determine their precise function in shaping distinct aspects of reward, motivation, decision-making and addiction. For this purpose, we have recently developed a novel knock-in mouse line expressing the Cre recombinase only in MOR-expressing neurons (Oprm1-Cre mouse). The Oprm1-Cre mouse allows us for the first time to genetically target exclusively the MOR+ neurons in defined brain regions.

We have already extensively characterized the specificity of the Oprm1-Cre mouse based on neuroanatomy, in situ hybridization and single-cell RNA sequencing, thereby establishing the feasibility of targeting MOR+ neurons using the new Oprm1-Cre mouse line.

We aim to define the functional role of mu opioid expressing neurons in basal ganglia circuits for reward processing and transition to addiction.
Grid cells in the entorhinal cortex fire in a triangular pattern that tessellates the surface of the surroundings. To be used as a spatial reference, the grid needs to anchor to the external world. The grid is not randomly oriented but displays geometrical regularities in relation to the environment. These regularities include a specific offset and an elliptical distortion that might be indicative of an anchoring process.

In this study we aim to characterize the shape of the grid on a local scale to investigate whether local features of the grid display specific relations to the walls and corners of the environment. Moreover, to further understand the role of these features in anchoring we also study how the grid evolves in a novel environment during the anchoring process.

Local feature maps were produced using a sliding window autocorrelation algorithm, permitting us to visualize changes in orientation, size and ellipticity of the grid throughout the environment. Most grid modules showed variations that were consistent with a barrel distortion, meaning that the grid in the middle of the box had larger spacing than closer to the corners. Furthermore, some animals displayed pentagonal distortions known as dislocations.

Analyses of the data from novelty experiments showed that the grid was not stable from the first exposure. Individual fields would sometimes move independently or in concert with neighboring fields.

To conclude, grid cells display rich dynamics during learning a new environment possibly reflecting how the entorhinal cortex uses sensory cues of the environment for anchoring.
In the medial entorhinal cortex (MEC), speed cells are a functionally distinct neuronal population, whose firing rates increase linearly as a function of locomotion speed. This speed signal is believed to be a key component for the dynamic update of grid cell activity; however, its origin has not been determined. Several studies have reported speed-coding neurons in the mesencephalic locomotor region (MLR), an area widely implicated in locomotion, but it remains unclear whether and how signals from these neurons reach the MEC. Here we combined classical anatomical tracing studies with chronic unit recording and optogenetics in freely moving rats to search for a putative speed circuit between the pedunculopontine tegmental nucleus (PPN), a functional component of the MLR, and the MEC. Simultaneous injections of a retrograde tracer in MEC and an anterograde tracer in PPN revealed strong overlap between labelled PPN axons and MEC-projecting cell bodies in the ventral medial septum and diagonal band of Broca (MS/DB). Chronic in vivo tetrode recordings during free foraging in an open field confirmed the presence of speed cells with linear speed-rate relationships at all three levels of the putative circuit – PPN, MS/DB, and MEC. Optogenetic stimulation of channelrhodopsin-2-expressing neurons in PPN was followed, at regular latencies, by activation of subsets of cells in MS/DB and MEC, including speed cells. Taken together, the results raise the possibility that the PPN-MS/DB-MEC circuit mediates the coding of a speed signal with a possible relevance for dynamic spatial mapping and navigation.
Acute cocaine administration in humans results in a brief but strong euphoria underlied by increased activation of the limbic areas.

Here we tested how the acute administration of cocaine influences locomotion as well as the expression patterns of the immediate early gene c-Fos throughout the brain. Two experimental groups of naïve mice received single intraperitoneal injection of either saline or cocaine (20mg/kg). Both groups were tested in the open field paradigm. Mice were sacrificed one-hour post injection and the serial slices of the whole brain were stained with c-Fos and dapi.

Primary results indicate that the default C-Fos expression is restricted to certain brain areas and the cocaine-induced C-Fos expression is increased throughout the brain. In the open-field test the cocaine-treated mice had increased locomotor activity accompanied by stereotyped moving patterns (i.e. following a clockwise direction only). We then performed mediational analysis to tease apart the relative contribution of c-Fos in different regions for generating cocaine-induced locomotion. Orbital cortex as well as dorsal striatum showed to mediate the effect of cocaine induced c-Fos expression on locomotion. Currently in vivo extra cellular recordings in awake and head-fixed mice are ongoing to validate these findings and tease apart the contribution of these regions to locomotion (motor output) versus Pavlovian conditioning of rewards (reward processing).
The medial entorhinal cortex (MEC) is a key brain structure for the navigational senses of animals. Recent years have seen the discovery of several functional MEC cell types that constitute essential components of a cognitive map, including head-direction cells, border cells, speed cells and grid cells. However, little is known about whether, or to what extent, cells in the MEC contribute to landmark-based navigational strategies. Such strategies might include using the perceived distances and directions to discrete environmental landmarks that, in most realistic environments, are abundant. We recorded the activity of single units in superficial MEC in the presence and absence of prominent three-dimensional objects and found that a proportion of MEC neurons tended to increase their activity robustly when the animal was located at a certain direction and distance relative to the object. This vectorial tuning to the object persisted when the object was displaced, and was shown to be consistent for multiple objects of different shapes and sizes. Moreover, we found that the characteristic responses of such object-vector cells were present from first exposure to the environment, and that directional tuning rotated coherently with the directional preferences of head direction cells during remapping, suggesting that object-vector cells are part of a universal and rigid entorhinal map. The majority of object-vector cells exhibited clear tuning regardless of the animals heading direction relative to the object, meaning that these cells encode distance and direction to prominent landmarks within an allocentric reference frame.
B10: Uppsala University Behavioral Facility (UUBF) has the capability and competence to conduct behavioral studies in mouse, rat and fish
- Å. Konradsson-Geuken, K. Kullander, E. Roman, S. Winberg

Presenter: Åsa Konradsson Geuken - Uppsala University
Theme: Integrative Physiology and Behavior
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Time of presentation: Thursday June 8 - 1200-1400

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Uppsala University Behavioral Facility (UUBF) is a non-profit core facility supported by the Faculty of Medicine and Pharmacy, Uppsala University. UUBF’s main aims are to provide administration- and organization services of behavioral tests for internal and external research groups. We offer a large array of behavioral tasks for mouse, rat and fish, e.g. tasks for exploration, motor behaviors, sensorimotor processing, learning, memory and behavioral profiling. UUBF provides equipment together with protocols for behavioral experiments, and assists with data analysis, interpretation, and advanced statistical analyses. We also provide assistance with writing of ethical applications and training and guidance in experimental design. Further, UUBF offers annual graduate courses on animal behavior e.g. “How to study behavior in vertebrates with focus on fish and rodents”. You are welcome to contact UUBF for discussing your future behavioral experiments.
Recent experimental studies on classical fear conditioning have revealed an inhibitory microcircuit in the central amygdala (CEA), which is essential for the acquisition and expression of conditioned fear. In these studies, subpopulation-specific changes in baseline firing rate and modulation of tonic inhibition, mediated by extra-synaptic GABA-receptors, have been shown to correlate with fear generalization. Here, we used mathematical analysis and numerical simulation of the central amygdala network to study the effects of tonic inhibition on the processing of transient inputs. The model corroborates experimental findings and allows for dissecting the link between tonic inhibition, baseline firing rates and network responsiveness, thereby providing a mechanistic explanation for the observed effect on fear generalization. In view of recent results linking fear generalization to anxiety, we discuss a possible role of the CEA in processing CS-US statistics during conditioning and adjusting sustained fear accordingly.
The Subthalamic Nucleus (STN) is the only glutamatergic area within the Basal Ganglia (BG), which plays an important role in the modulation of motor functions given its excitatory action onto the output structures of the BG in the so called indirect pathway. Lesion of the STN, as well as Deep Brain Stimulation (DBS), can ameliorate hypokinetic symptoms in Parkinsonian patients. Besides the positive effect in alleviating motor deficits, STN DBS is also responsible for different side effects related with affective functions. However the action mechanism underlying DBS and which circuit elements are responsible for its therapeutic and side effects are still unknown. To target a specific STN neuronal population we used a genetic approach, by which neurons are rendered light-sensitive by delivering conditional recombinant adeno-associated virus (rAAV) vectors carrying opsin genes bilaterally in the STN of transgenic mice expressing Cre recombinase under the control of Pitx2 promoter. We used a continuous 535 nm light stimulation to precisely inhibit these Cre-expressing cells in mice injected with rAVV carrying archaerhodopsin-3 (Arch). Histological analysis display strong virus expression in all the already described STN-target areas. Preliminary results from opto-behavioral experiments suggest an involvement of this population of neurons in affective functions.
Lateral habenula (LHb) have been implicated in both reward-seeking behavior and in depressive disorders due to its modulatory effects on dopamine and serotonin reach areas. Excitatory projections from LHb target GABAergic interneurons of both ventral tegmental area (VTA)/rostromedial tegmental nucleus (RMTg) and dorsal raphe nucleus (DR) providing strong inhibition on both dopaminergic and serotonergic systems. These reward-related signals are provided to LHb from distinct neuronal populations in basal ganglia.

Here we provide an anatomical characterization of the glutamatergic inputs to LHb, by specific retrograde and transsynaptic labeling, with a two-vector system that farther reveals the direct monosynaptic inputs to this population. Behaviorally, optogenetic stimulation of this glutamatergic inputs to LHb induce a strong avoidance response as it is demonstrated in behavioral tests such as place preference and operant conditioning paradigms. Furthermore we provide a characterization of the firing pattern of these neurons during reward related behaviors with in vivo calcium imaging in freely moving animals.

Taken the importance of LHb as a modulatory nucleus of the dopaminergic and serotonergic systems the definition of its connectivity and function will give valuable insights in the understanding of both reward-seeking behavior and depressive disorders.
Karsten Specht, University of Bergen

Music can trigger emotional responses in a more direct way than any other stimulus. In particular, music-evoked pleasure involves brain networks that are part of the reward system. Furthermore, rhythmic music stimulates the basal ganglia and may trigger involuntary movements to the beat. In the present study, we created a continuously playing rhythmic, dance floor-like composition where the ambient noise from the MR scanner was incorporated as an additional instrument of rhythm. A second group of participants were scanned without any additional stimulation and were not informed that they took part in a study on rhythm.

The analysis was twofold: First, a whole-brain independent component analysis (ICA) was conducted. Only components that showed group differences in their time-frequency spectrum were further analysed. Second, data was analysed with stochastic dynamic causal modelling (sDCM) in order to explore functional dependencies and interactions between core areas of auditory perception, rhythm processing (putamen/pallidum), and reward processing (ventral striatum/nucleus accumbens).

Compared to the control group, both analyses demonstrated consistently an increased activity as well as an altered connectivity of the reward system, i.e. the right ventral striatum/nucleus accumbens. Further, the DCM analyses demonstrated a reduced connectivity within the basal ganglia, as well as a reduced functional connectivity of the right ventral striatum/nucleus accumbens from and to the basal ganglia and auditory network while listening to rhythmic music.

These converging results may indicate that the dopaminergic reward system reduces its functional connectivity and relinquishing its constraints on other areas when we listen to rhythmic music.
Abstract

The ventral tegmental area consists of dopaminergic and glutamatergic neurons that are associated with reward and aversion. A subset of midbrain dopamine neurons express the vesicular glutamate transporter 2 (VGluT2), which enables them to package and release glutamate. Several studies have shown that ablating VGluT2 in these co-releasing cells during development results in altered locomotor activity in response to psychostimulants and enhanced drug-seeking behavior towards natural rewards or drugs of abuse. These behavioral manifestations may however be coupled with potential developmental abnormalities as a result of embryonic deletion of VGluT2. The aim of the study was to investigate the role of glutamate co-release from dopamine neurons in the adult mouse.

We now demonstrate that targeting VGluT2 in the dopamine neurons of adult mice results in increased consumption of natural rewards (sugar) without any differences in the levels of potassium-evoked dopamine release in the dorsal and ventral striatum. Further, patch-clamp recordings of medium spiny neurons of the ventral striatum shows that targeting glutamate co-release from mature dopamine neurons results in downstream postsynaptic alterations.

Overall our findings suggest that loss of VGluT2 from this co-releasing population results in alterations in striatal synaptic plasticity and reward associated-behaviors when ablation occurs in the adult mouse.
The endocannabinoid system is a lipid signaling network that modulates numerous biological processes, including neurotransmission and immune function. The major endogenous agonists (i.e., endocannabinoids) for cannabinoid receptors CB₁ and CB₂ are the arachidonic acid derived lipids 2-arachidonoyl glycerol and N-arachidonoyl ethanolamine (anandamide). Altered endocannabinoid signaling in the brain has been implicated in nociception, learning and memory, anxiety, depression, emotion and reward. The indirect modulation of endocannabinoid levels may lead to less side effects than the direct activation of CB₁ receptors in terms of neurotransmission, metabolism and immunomodulation.

The extracellular effects of the endocannabinoids anandamide and 2-arachidonoyl glycerol are terminated by enzymatic hydrolysis after crossing cellular membranes by facilitated diffusion. The lack of potent and selective inhibitors for endocannabinoid transport has prevented the molecular characterization of this process, thus hindering its biochemical investigation and pharmacological exploitation. Here, we report the design, chemical synthesis, and biological profiling of natural product-derived N-substituted 2,4-dodecadienamides as the first selective endocannabinoid uptake inhibitors. The highly potent (IC₅₀=10 nM) inhibitor N-(3,4-dimethoxyphenyl)ethyl amide (WOBE437) exerted pronounced cannabinoid receptor-dependent anxiolytic, anti-inflammatory and analgesic effects in mice by increasing endocannabinoid levels. A tailored WOBE437-derived diazirine-containing photoaffinity probe (RX-055) irreversibly blocked membrane transport of both endocannabinoids, providing first mechanistic insights into this complex process. Moreover, RX-055 exerted potent site-specific anxiolytic effects upon in situ photoactivation in the brain. This study describes the first suitable inhibitors to target endocannabinoid membrane trafficking and uncovers a novel endocannabinoid pharmacology.

Reference:
Chicca, A. et al., Proceedings of the National Academy of Sciences (PNAS) (2017), under revision
Recent optogenetic circuit manipulation studies suggest that GABAergic and glutamatergic lateral hypothalamus populations contribute to appetitive and aversive behavior in mice. Aversive responses evoked by photoexcitation of glutamatergic LH neurons appear to be effected in part via projections to the lateral habenula (LHb), a structure thought to contribute to appetitive and aversive stimulus processing and aversive learning. To further investigate the role of glutamatergic LH neurons in valence-coding, we endeavored to characterize the endogenous activity of glutamatergic LH populations during appetitive and aversive stimulus processing. To realize our aim, we employed miniaturized, head-mounted microendoscopes (Inscopix) to image calcium transients within the LH of freely behaving mice. Using viral vectors and transgenic Vglut2-Cre animals, we targeted the calcium indicator GCaMP6 either to all glutamatergic LH neurons, or specifically to the LHb-projecting population. Within both the general, and the projection-specific groups, we observed neurons responding to reward-delivery, foot-shocks, and shock-predicting tones. Critically, LHb-projecting glutamatergic neurons appear to prefer the aversive stimuli, supporting the notion that this population contributes to LHb’s aversive valence-coding.
Cortical inhibitory interneurons have a vital role in modulating cortical output and plasticity. Dysfunction in cortical interneurons expressing parvalbumin (PV) is implicated in the pathophysiology of a range of neuropsychiatric disorders, and changes in brain-derived neurotrophic factor (BDNF) - tyrosine receptor kinase B (trkB) signaling in cortical PV interneurons have been associated to pathophysiology in schizophrenia. Furthermore, truncated trkB isoforms, unable to mediate normal neurotrophic response, have an increased expression in schizophrenic patients. The changed expression is correlated with altered GABA inhibition and local network synchronization.

The medial prefrontal cortex (mPFC) is pivotal to cognitive and emotional processing, and aberrant prefrontal activity is thought to underlie decreased cognitive abilities in neuropsychiatric disorders and addiction. To directly investigate how BDNF-trkB signaling in prefrontal PV interneurons regulate emotional and cognitive processing we generated adeno-associated viruses with Cre-dependent expression of a dominant negative trkB receptor (trkB.DN; a truncated receptor that binds to BDNF but does not trigger intracellular signaling cascades). Adult PV-Cre mice injected with trkB.DN into the mPFC display normal locomotion but show aggressiveness and disturbances in behaviors related to memory, fear and anxiety. In vivo recordings reveal that the behavioral phenotypes are associated with changed oscillatory activity during sleep-states. We are currently performing recordings of PV interneurons and pyramidal neurons in mPFC in awake and behaving animals.

We hope that our study will contribute to the understanding of the relationship between BDNF-trkB signaling in cortical interneurons, behavioral alterations relevant to schizophrenia and aberrant states of prefrontal hyperactivity in neuropsychiatric disorders.
The Ventral Tegmental Area (VTA) is the area of the midbrain where the cell bodies of A10 dopamine neurons are located and where the mesocortical and mesolimbic pathways originate. The region has been extensively studied in the context of reward-related behaviors and it has been implicated in several pathological conditions as addiction, food intake disorders and depression. In contrast to long-standing beliefs, the VTA has been found to be less homogeneous than only containing dopamine neurons. Instead, recent studies have demonstrated that in addition to dopamine cells, the VTA also comprises neurons that utilize glutamate or GABA as neurotransmitters, as well as co-releasing neuronal subpopulations. The precise roles of different VTA subpopulations in behavior is still unclear.

In our studies, we utilize optogenetics in a range of transgenic mouse lines that express Cre within various dopamine and glutamate neurons to selectively target their activity with laser stimulation. By implementing behavioral optogenetics in combination with standard experimental psychology tests, we perform real-time conditioned place preference (RT-CPP) and operant self-stimulation (SS) analyses to assess the effect of activation of these specific cell types in reward-related behaviors. We observed that dopamine and glutamate subpopulations have distinct projections and that the optogenetic stimulation can oppositely affect behavior; activation of dopamine cells induces reward while stimulation of those that utilize glutamate induces aversion. Our results provide valuable insight into the heterogeneity of the VTA and provide knowledge that could potentiate the search for more selective therapeutic approaches in disorders where the VTA is involved.
Locomotion is characterized by repetitive activity of muscles that displace the body in space. The neurons, network structure, and mechanisms that give rise to rhythmic activity in the mammalian motor system are not fully understood. Glutamatergic Shox2- and Hb9-interneurons play an important role in rhythm-generation in mammals (Dougherty et al. 2013; Calderia et al. 2017). However, an in vitro minimal inhibitory network can also evoke rhythmic activity in presence of drugs and absence of glutamatergic neurotransmission (Talpalar et al 2011). To resolve these issues, we studied generation of rhythmic activity both in vitro and in vivo using mouse genetics, electrophysiology and behavioral methods. Inactivation of all spinal glutamatergic neurons produced rhythmic activity in vitro (n=12) but was associated with limb paralysis and lack of postural activity in vivo (n=14), indicating that excitatory neurons are necessary for locomotor function in intact animals. Inactivation of dorsal spinal glutamatergic interneurons produced ataxia and slow locomotion, but not essentially changed other locomotor features (n=7). Inactivation of subpopulations of neurons in particular the Shox2-derived glutamatergic neurons preserved locomotor pattern in vitro and in vivo but reduced its frequency (n= 7). Inactivation of glutamatergic Hb9-interneurons preserved in vitro rhythmic activity but showed lack of hindlimb locomotor activity in vivo (n=5). We conclude that ventral spinal glutamatergic neurons are essential for locomotion in vivo. Shox2-interneurons are necessary for eliciting high but not low frequency locomotor activity. Glutamatergic Hb9-interneurons are essential for execution of rhythmic motor activity in the hindlimbs but not forelimbs.

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The striatum, the largest nucleus of the basal ganglia, plays an important role in motor planning, decision-making, motivation and reward. Alterations in its functionality can lead to several neurological disorders including Parkinson’s disease, Huntington, Obsessive-compulsive disorder, and addiction. The most abundant striatal neurons are the Spiny Projecting Neurons (SPNs) that comprise 95% of the neuronal population. The remaining 5% are locally-projecting interneurons that although less in number play a key role in regulating the output from the SPNs in the striatum through feedforward inhibition. The interneuron populations can be divided into several subtypes including the largest heterogeneous population expressing 5HT3a that we recently identified (Muñoz-Manchado et al., Cereb Cortex 2016; Gittis and Kreitzer, Trends Neurosci, 2012; Silberberg and Bolam, Curr Opin Neurobiol 2015). These studies point towards that the diversity of neuronal subtypes has been underestimated.

In order to elucidate this diversity we have taken advantage of a recent developed technique, such as the large-scale single cell mRNA sequencing (Zeisel, Muñoz-Manchado et al., Science 2015). We have performed a study of 1135 cells in the striatum with the molecular characterization of all interneuron subpopulations providing new markers also for previously described ones. With this approach we now have a vast database with the gene expression composition of each cell type in the striatum. We have validated this data with in situ hybridization and we have also applied another recent developed technique “patch-seq” in selected populations in order to investigate how the electrophysiological profile is directly linked to their transcriptome.
Vestibulospinal neurons are organized into discrete groups that project from the brainstem to either the ipsilateral or the contralateral side of the spinal cord, enabling animals ranging from agnathans to humans to maintain proper balance and posture. Our previous studies in the mouse and chicken have demonstrated that the ipsilateral lateral vestibulospinal tract (LVST) group derives from rhombomere (r)4, the contralateral medial vestibulospinal tract (cMVST) group derives from r5 and part of r4.

To characterize differential transcription factor expression in the LVST and cMVST, we performed RNAseq analysis on manually sorted retrogradely labeled LVST and cMVST neurons in embryonic day (E) 13.5 mice and embryonic day (d) 7.5 chickens. RNAseq of more medial regions of r4 and r5 was included as control groups. Highly differentially expressed transcription factors were further investigated by immunohistochemistry and 3D reconstruction at E13.5-15.5 in the mouse and d7.5-9 in the chicken.

RNAseq analysis revealed over 100 differentially expressed transcription factors, and immunohistochemistry corroborated the same group-specific expression patterns for several of these in the two species, including patterns that defined intragroup subpopulations. In the mouse, a specific set of 4 TFs was expressed in nearly all LVST neurons, and a distinct set of 4 TFs was expressed in nearly all cMVST neurons.

These data provide new information about the transcription factors that differentially specify the two vestibulospinal neuron groups and that define distinct neuron subpopulations within them.
Efficient spatial navigation is computed across several brain regions integrating information about past, present, and future positions. Posterior-parietal (PPC) and premotor (M2) cortices encode movements in egocentric coordinates and presumably synthesize behavioral trajectories to reach goals. Recent work has shown that PPC and M2 in rodents exhibit tuning for impending movements, but how these regions interact to produce movement plans during free behavior is poorly understood. To address this we are recording neural correlates of ongoing and future behaviors in PPC and M2 in rats foraging in an open arena. To obtain an unprecedentedly clear picture of the animals’ behavior we are tracking the head and spine using a 3D tracking system. Our analyses confirm previous reports of whole-body self-motion coding as visualized in 2-dimensional movement maps, but the 3D tracking data now reveal that cells in both PPC and M2 can exhibit fine tuning for different bodily effectors, in some cases independently of self-motion. We found cells in both PPC and M2 selective for specific degrees of pitch and roll of the head, while other cells are highly sensitive to azimuth and pitch of the back. We are currently investigating prospective coding of 3D movements across PPC and M2, and are investigating whether the relative coding properties across areas are maintained during different behaviors in a goal-oriented well-searching task. Our results are beginning to provide a first-time view of how the cortical motor system constructs self-guided, goal-directed behaviors in their native 3D.
Serotonin (5-HT) has been shown to have a distinct spinal motor influence. It was now the aim of the studies to evaluate if the spinal motor effects of L-DOPA and naloxone are possibly mediated by a serotonin interaction. The interstitial serotonin concentration in the spinal gray matter was determined using the microdialysis/HPLC method. In parallel with monosynaptic reflex testing in an alternating sequential procedure different FRA reflex pathways (low threshold cutaneous, group II muscle, nociceptive cutaneous) to the flexor PBSt and to the extensors GS and PI were tested, whereby the nociceptive pathway to the latter is an excitatory non-FRA pathway. After i.v. injection of L-DOPA (100 mg/kg) the spinal reflex effects started within 6-20 min with a maximum at about 30-50 min, while the serotonin concentration started to increase a bit later (6-27 min) and had its maximum with a delay of up to about 100 min. After i.v. injection of naloxone the serotonin concentration started to increase quite fast (1-5 min) and had its maximum already with a delay of about 5-10 min. This time course largely resembles the time course of the reflex effects. The difference of the time course of the increase of the L-DOPA induced serotonin concentration compared to the time course of the L-Dopa induced changes of the spinal reflex effects renders a direct causal interrelation quite improbable, while the similar time courses of the naloxone induced increase of serotonin concentration and the spinal reflex effects do not completely exclude such an interrelation.
Cerebrospinal fluid-contacting (CSF-c) cells are present in the walls of the ventricles and the central canal and found throughout the vertebrate phylum. We recently identified ciliated somatostatin/GABA-expressing CSF-c cells in the lamprey spinal cord that act as pH sensors. Acidic and alkaline responses were recorded in the same cell, mediated through ASIC3 and PKD2L1 channels, respectively (Jalalvand et al 2016). Here, we investigate if the ciliated somatostatin/GABA-positive CSF-c cells in the hypothalamus have similar properties to their spinal counterparts by performing whole-cell recordings in hypothalamic slices. Depolarising current pulses readily evoked action potentials, but hypothalamic CSF-c neurons had no or a very low level of spontaneous activity at pH 7.4. They responded, however, with depolarisation and trains of action potentials to small deviations in pH, in both the acidic and alkaline direction. Like in spinal CSF-c neurons, the acidic response in hypothalamus is mediated via ASIC3. In contrast to spinal CSF-c neurons, the alkaline response appears not to depend on PKD2L1 channels. The CSF-c neurons extend their processes dorsally, ventrally and laterally, but as yet we do not know the effects exerted on the hypothalamic circuits. Dopaminergic CSF-c neurons just at the obex also respond in a similar way to acidic and alkaline pH. They fire spontaneous action potentials and display excitatory and inhibitory postsynaptic potentials. The glutamate and GABA receptor antagonists could block most of the EPSPs and IPSPs. The pH-sensing ability of hypothalamic CSF-c neurons and spinal cord are likely to have been conserved through vertebrate phylogeny.
Neural circuits in the brain typically consist of thousands of neurons. Intuitively, this would suggest that in order to describe the spiking rates in such a circuit one would correspondingly need thousands of variables. However, electrophysiological recordings from a range of different brain areas and across different species suggest that the neural activity is correlated in such a way that only a handful of variables are actually required. Mathematically, this can be seen as the activity being confined to a manifold or hyperplane of the neural state space. In theoretical neuroscience, the observation has raised the question of what kind of connectivity could give rise to such manifolds, as they do not arise spontaneously in homogeneous, randomly connected networks.

In this work, we show that having the spike rates confined to a manifold is consistent with a class of previously proposed models of neural computations. In particular, we demonstrate that by using one of these models – the Neural Engineering Framework – one can gain fine-grained control of the dimensionality (i.e. the number of required variables) of the manifold. Furthermore, our adaptation of the model handily explains why the manifold not only emerges in biological networks, but also itself restricts what neural patterns can be learned, as recently shown in a prominent BCI study. Finally, we show that the connectivity stemming from the model is biologically plausible with respect to several important features, including a heavy-tail distribution of synaptic weights.
Neuroprotection at the initial stage of spinal cord injury (SCI) is one main goal to inhibit delayed network damage triggered by excitotoxicity mediated via hyperactivation of glutamatergic systems. Previous studies have shown positive effects of general inhalation anesthetics, while early neurosurgical operations can attenuate late pathophysiological events. It is interesting to find out if the widely used i.v. anesthetic propofol could protect locomotor spinal networks from excitotoxic insult induced by transient application of kainate (0.1 mM) for 1 h to the rat spinal cord in vitro. This protocol was designed to mimic the clinical onset of SCI followed by intensive care management. Significant neuronal losses were elicited by kainate, with almost halving of motoneuron numbers. Bath-applied propofol (5 µM, 4-8 h) potentiated GABA and depressed NMDA receptor responses together with decreased polysynaptic reflex activity which partially recovered after 24 h. Fictive locomotion evoked by repeated dorsal root stimuli or NMDA and serotonin (5HT) was weaker; however, when applied after kainate, there was no additive depression on synaptic transmission, suggesting that any further deterioration had been arrested. In all spinal areas and especially in the motoneuron pools, significant neuroprotection was observed after propofol administration following kainate. The periodicity of disinhibited bursts was improved by propofol after the kainate insult in line with the good histological preservation. These results suggest propofol could exert a delayed neuroprotective action on spinal network excitotoxic damage in an in vitro SCI model.
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Locomotor movements are generated by spinal locomotor networks and require the coordinated recruitment of motor neuron pools to drive muscle contractions in an appropriate sequence. Different motor units need to be engaged successively from slow to intermediate and fast to increase the locomotor speed. Presumably, specific rules of convergence of synaptic drive from premotor excitatory interneurons are needed to dictate the sequence of activation of motor neurons. However, the nature of the convergence and the dynamics of the excitatory inputs to identified motor neurons are still unclear.

We have addressed these issues in the adult zebrafish in which the locomotor circuit is organized in three sub-circuit modules with sub-classes of the excitatory V2a interneurons connecting selectively to slow, intermediate or fast motor neurons. We sought to determine the rules of convergence of V2a interneurons that reliably control the recruitment of motor neurons of the slow, intermediate and fast sub-circuits. Our results show that the convergence rule varies among the three sub-circuits. In addition, there were differences within each sub-circuit depending on the firing properties of the presynaptic V2a interneurons. Indeed, V2a interneurons either displayed intrinsic burst or tonic firing. The bursting V2a interneurons target the motor neuron dendrites to elicit large EPSPs, while the tonically firing ones have bifurcating axons targeting the soma to produce relatively smaller EPSPs. During each V2a interneuron burst there was super linear EPSP summation that was highest in the slow sub-circuit module and lowest in the fast module and required activation of NMDA receptors. These properties ensured the fidelity and strength of the transfer of excitatory drive within each sub-circuit module and hence a module-specific convergence rule. In the slow module the convergence of only two V2a interneurons was required to engage the corresponding motor neurons. The intermediate module required the convergence of 6 V2a interneurons, while the fast module necessitated more than 40 interneurons to ensure motor neurons recruitment. Thus, this study reveals the rules of convergence that in combination with the NMDA-induced super linear synaptic dynamics ensure the sequential activation of motor neurons of three sub-circuit modules to increase the locomotor speed.
Recently, high frequency oscillations have been observed at the level of individual neurons firing and local field potential in the striatum of both awake and anaesthetized animals [1-4]. It is quite likely that the experimentally observed oscillations in the striatum are in fact cortical oscillations transmitted by the cortico-striatal projections. However, there is limited knowledge about the exact nature of this routing process and therefore in this study we use a network model of the striatum to elucidate the importance of specific GABAergic neurons in shaping striatal oscillatory activity.

Fast spiking interneurons (FSIs) are a common property of neuronal networks throughout the brain [5]. In the striatum despite their high firing rates, FSIs do not seem to play a major role in controlling the firing of medium spiny neurons (MSNs) [6] and so far, it has not been possible to attribute a functional role to FSIs in the striatum. We propose that FSIs can perform an important role in transferring cortical oscillations to the striatum especially to those MSNs that are not directly driven by the cortical oscillations. Further, the variables such as the number of activated neurons, ongoing activity, connectivity, and synchronicity of inputs influence the transfer of oscillations by modifying the levels of FB and FF inhibition. Our results support the idea of the precise orchestration of FSI activity that plays a key role in determining the pattern of the firing of MSNs, which might provide optimal integration of external inputs into striatal network.

References

The optic tectum (superior colliculus in mammals) is a conserved region that integrates different sensory modalities (which are species dependent), and controls gaze movements through excitatory output neurons projecting to the brainstem. Tectum can perform stimulus selection independently and accordingly redirect gaze, but it can also be influenced by extrinsic brain sources – including pallium (cortex in mammals) and basal ganglia. Here we show that the lamprey homologue of the mammalian SNc/VTA sends direct projections to tectum that modulate its sensorimotor integration, suggesting that the nigral dopaminergic control of motor responses is more complex than generally assumed, involving additional pathways to the widely studied striatal projection. D1 and D2 dopamine receptors are expressed in tectum in separate neuronal populations, as shown by patch-clamp recordings. Dopamine increases the excitability of D1 expressing cells and decreases the excitability of D2 cells. Dopamine therefore changes the responsiveness to sensory inputs reaching the optic tectum making them more or less effective in evoking a motor command. Using a novel eye-brain preparation, we show that local dopamine agonist injections in tectum affect eye and trunk movements, by recording eye muscles and ventral root activity in response to natural stimuli applied with a screen. Our results show that dopamine directly modulates motor responses mediated by tectum. Given the high degree of conservation of the midbrain and basal ganglia, and the presence of direct dopaminergic projections from SNc to the superior colliculus in rodents, this previously unexplored mechanism is likely to also be present in higher vertebrates.
The posterior parietal cortex (PPC) is a multifaceted region of cortex, contributing to several cognitive processes including sensorimotor integration and spatial navigation. Our knowledge of PPC function is founded on neurophysiological recordings in primates, though recent years have seen a rise in the use of rodent models, particularly mice, to study PPC and related networks. While murine models bring several technical advantages including large-scale recordings and calcium imaging, the anatomical locus of PPC in mice remains ill-defined. To address this we have taken multiple approaches to delineate PPC in the mouse and establish its connectivity. We first used corresponding nissl- and parvalbumin stained sections to delineate mouse PPC based on cytoarchitectural criteria that distinguish PPC from surrounding regions. Secondly, based on coordinates from our study of the cytoarchitecture, we targeted the mouse PPC with retrograde tracers, including cholera toxin B and rabies virus. We found that the complement of cortical inputs to mouse PPC closely matches that described in rats, including predominant inputs from visual, cingulate, retrosplenial and secondary motor cortices. Lastly, a work currently in progress is to define the boundaries of mouse PPC based on patterns of inputs from primary visual cortex (V1). This involves co-injections of multiple anterograde tracers into V1, and to delineate the patterns of fiber termination in coronal sections. By comparing tracer staining and cytoarchitecture we aim to obtain a coherent definition of mouse PPC incorporating laminar anatomy and visual cortical inputs.
One of the most remarkable abilities of the human mind is to consciously simulate actions without physically executing them. Since the late 1980s, research on motor imagery has identified several similarities between imagined and executed actions at the behavioral (Decety et al., 1989; Decety and Jeannerod, 1995), physiological (Decety et al., 1991, 1993) and neural level (Ehrsson et al., 2003; Grezes and Decety, 2001; Hétu et al., 2013), supporting their functional equivalence (Jeannerod, 1994, 2008). In sharp contrast, little is known about their computational equivalence —namely, the involvement of forward models (Miall and Wolpert, 1996; Wolpert and Flanagan, 2001; Davidson and Wolpert, 2005; Blakemore and Sirigu, 2003; Grush, 2004; Ridderinkhof and Brass, 2015). Here, we tested whether motor imagery allows for sensory attenuation i.e., a phenomenon wherein sensory stimuli that are predicted by the forward models based on a copy of the motor command (efference copy), feel less intense than identical stimuli of external origin (Bays and Wolpert, 2008; Wolpert and Flanagan, 2001). We show that the perception of touch is attenuated when presented as the outcome of an imagined movement. Moreover, the imagery-induced attenuation has the same magnitude and follows the same spatial principle as veridical movement-induced attenuation. Our results demonstrate that motor imagery engages forward models to predict the sensory consequences of the imagined movements just as physical movements do. This finding supports the notion of "computational equivalence" between imagined and executed movements.
Locomotor-initiating signals from the midbrain are funneled through neurons in the reticular brainstem formation to reach the spinal locomotor circuits. The aim of this study is to identify the brainstem neurons forming the final command signal, the "go" signal, that initiates over-ground locomotion with the ultimate aim of identifying the mechanism for how spinal locomotor circuits are activated from the brainstem. For this we have used detailed mapping of locomotor-initiating areas in the pons and hindbrain using an in vitro brainstem-spinal cord preparation of neonatal mice. We find a restricted area in the caudal half of the brainstem, with sharp mediolateral boundaries where low threshold unilateral electrical stimulation (ES) evokes coordinated locomotor-like activity which resembles locomotor behaviors observed in vivo. The locomotor frequency is modulated with the frequency of ES and generally faster than that evoked by drug-application in the spinal cord. Optogenetic experiments show that activation of glutamatergic neurons in the ES-defined area evokes locomotor-like activity similar to the ES-evoked one, suggesting that glutamatergic neurons are involved. When glutamatergic transmission is blocked in the brainstem, the cervical, and thoracic spinal cord, both optogenetic and electrical stimulation still evokes locomotor-activity in the lumbar spinal cord. These results suggest that excitatory reticulospinal neurons can activate the locomotor networks in the lumbar spinal cord directly to initiate locomotion. Our study localize the "go" signals to a restricted area of the brainstem and provide means to functionally define the cellular targets of "go" signal in the spinal locomotor networks.
For neuronal circuits in the spinal cord (SC) that control locomotion, developmentally expressed transcription factors (TF) have served as entry points for functional assignment of left-right and flexor-extensor coordination circuits, as well as rhythm-generation circuits. It is clear though that these functions are most often represented by molecularly heterogeneous groups of neurons that might also only partly capture the function. For rhythm-generation several glutamatergic molecularly defined groups of cells are thought to be involved without any of them creating the function alone. In order to capture new markers for this important groups of neurons in the SC we have performed FACS sorting, RNA-sequencing and differential expression analyses on glutamatergic neurons from the mouse ventral SC. We compared the postnatal expression profile of all glutamatergic neurons in the SC, the Vglut2-expressing neurons, to that of non-glutamatergic neurons as well as to one of the glutamatergic subgroups so far linked to rhythm-generation, the Shox2 interneurons (Dougherty et al. 2013). Amongst the transcripts up-regulated in the Vglut2-expressing neurons are well-known glutamatergic developmental-markers such as Sim1, Evx2, Lhx3, Chx10, Shox2 and Lbx1. The analysis also identified more then 200 receptors, TFs, and ion-channels specifically expressed in glutamatergic neurons as compared to non-glutamatergic neurons and Shox2-interneurons. Our findings identify novel glutamatergic subgroups in the SC and provide tools for further specification of SC motor functions. In addition, since glutamatergic neurons are found throughout the nervous system, this work might provide new molecular entry points to glutamatergic neurons in general.

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Locomotion can be adapted to different behavioral goals and performed in different directions (walking forward (FW), backward (BW), etc.). In the present study we compared kinematics of FW and BW performed by mice on different setups: in tunnel, on treadmill and on air ball. We found that mice could walk with three different body configurations: the hip high above the ground and the rostrocaudal range of toes movements symmetrical in relation to the hip projection (HP) to the surface (symmetrical steps); the hip low and the range of toes movements shifted either rostrally (rostral steps) or caudally (caudal steps) in relation to HP. During BW, only rostral stepping was observed. During FW, types of stepping were different on different set-ups. Cycle duration and stride length varied in a wide range and did not depend on set-up and type of stepping. Averaged swing duration was twice shorter during BW than during FW. Movements at the hip joint were generally simple: flexion during FW swing - extension during stance, and extension during BW swing - flexion during stance. However, a reversal in the direction of movement slightly preceded the moments of transition from swing to stance and from stance to swing during FW but was slightly delayed during BW. Movements at knee and ankle joints strongly depended on the type of stepping (rostral/symmetrical/caudal). They were coordinated to keep the hip joint approximately at the same height during stance and to make the limb length minimal when toes were passing HP during swing.

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Keywords: locomotion, backward, intralimb coordination, interlimb coordination, body configuration
While cholinergic neuromodulation is important for locomotor circuit operation, the specific neuronal mechanisms that acetylcholine employs to regulate and fine-tune the speed of locomotion are largely unknown. Here, we show that cholinergic interneurons are present in the zebrafish spinal cord and differentially control the excitability of distinct classes of motoneurons (slow, intermediate and fast) in a muscarinic dependent manner. Moreover, we reveal that m2-type muscarinic acetylcholine receptors (mAChRs) are present in fast and intermediate motoneurons, but not in the slow motoneurons, and that their activation decreases neuronal firing. We also provide evidence that this configuration of motoneuron muscarinic receptors serves as the main intrinsic plasticity mechanism to alter the operational range of motoneuron modules. These unexpected findings provide new insights into the functional flexibility of motoneurons and how they execute locomotion at different speeds.
Cholinergic Interneurons (ChINs) are a small population of interneurons in the mouse striatum. Expressing the neurotransmitter Acetylcholine, these neurons are the main population of excitatory interneurons in the Striatum. The role of the ChINs in Striatal function is not yet fully understood, but can be explored by studying their connectivity.

While ChINs do not appear to contact each other monosynaptically, they do exhibit an exceptionally strong disynaptic connection (1). A single action potential induced in a presynaptic ChIN can elicit a strong GABAergic input to multiple nearby ChINs, mediated by an unknown intermediate. A similar disynaptic connection targeting Medium Spiny Neurons has been reported to be mediated by axo-axonal targeting of Dopaminergic fibers originating in the midbrain (2). As these Dopaminergic terminals co-release GABA (3), we investigated their role in mediating the disynaptic inhibition between Striatal ChINs.

We combined pharmacological and optogenetic modulation of Dopaminergic axon terminals in the striatum to test how midbrain Dopaminergic neurons affect the ChINs disynaptic pathway. Using whole-cell patch clamp recordings, we were able to directly measure alterations in synaptic strength as well as failures to elicit synaptic transmission by the presynaptic ChIN following Dopamine receptor activation. Our results suggest that optogenetic stimulation of Dopaminergic terminals induces a short interval during which the disynaptic pathway is suppressed and cannot be elicited by even strong activation of ChIN axons. Importantly, inactivation or ablation of dopaminergic axons does not impair the disynaptic pathway, implying that although midbrain dopamine neurons can modulate the disynaptic connection between striatal ChINs, they do not mediate it. Our results suggest a novel form of interaction between the dopaminergic and cholinergic systems at the level of the striatal microcircuitry.


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Higher vertebrates can walk not only forward (FW) but also backward (BW), sideward, etc. Basic locomotor mechanisms reside in the spinal cord. Spinal locomotor networks can be activated by signals from the brainstem, as well as by epidural electrical stimulation of the spinal cord (ES). Our previous results suggest that the locomotor system includes two principal mechanisms: one generating the vertical component of step (limb elevation and lowering), and another one - the horizontal component (horizontal limb transfer). The aim of the present study was to reveal spinal neurons contributing to generation of vertical and horizontal components of step. With this purpose, in the decerebrate cat preparation, we recorded activity of the same individual spinal neurons in L4-L6 during treadmill FW and BW walking evoked by ES of the spinal cord. In addition, the same neurons were recorded during FW walking evoked by stimulation of the mesencephalic locomotor region (MLR) and by ES.

We found that neurons had the same phase of modulation during FW walking evoked by MLR-stimulation and by ES. Neurons recorded during both FW and BW walking were divided into three groups according to their activity: Group 1 (the same phase of modulation during FW and BW walking), Group 2 (modulated only during FW or only during BW walking), Group 3 (the phase of modulation depending on the locomotion direction). We suggest that Group 1 belongs to the network generating the vertical component of steps, while Groups 2 and 3 – to the network generating the horizontal component.

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Keywords: words: locomotion, backward, spinal neurons, decerebrate cat, epidural spinal cord stimulation, mesencephalic locomotor region
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Flexibility in the bilateral coordination of muscle contraction underpins variable locomotor movements or gates. The left-right coordination during locomotion can vary in a context-dependent manner to produce alternation through the activity of commissural interneurons connecting local interacting circuits on the two sides of the spinal cord. The V0 interneurons represent a major commissural neuronal population comprising dorsal excitatory (V0v) and ventral inhibitory (V0d) classes. The current view of V0 function derives from studies in immature motor systems (larval zebrafish and newborn mouse), but the activity patterns of V0d and V0v classes is unknown. Here we examined how the activity of the V0v interneurons varies with the speed of locomotion in adult zebrafish. Our results show that although V0v interneurons express a defined transcription factor and transmitter phenotype, their activity patterns during locomotion are heterogeneous. V0v interneurons could be segregated into two distinct types based on whether or not they display rhythmic activity during locomotion. The rhythmically active V0v interneurons could be further subdivided into three main sub-classes engaged sequentially during swimming, first at slow then intermediate and finally fast locomotor speeds. The order of recruitment of the three sub-classes of V0v interneurons is defined by a combined computation of their synaptic drive and intrinsic properties. The extent of the rhythmic excitation is the result of a scaling of the synaptic current with the input resistance of the different V0v interneurons. This study thus uncovers, for the first time in an adult vertebrate, an important organizational principle for a key class of commissural interneurons and the underlying cellular and synaptic mechanisms defining their pattern of recruitment as a function of locomotor speed.
An increasing number of studies indicates that spatial (re-)organization, e.g. clustering, of dendritic spines occurs during learning. The co-activation of spatially clustered spines in distal dendrites can also cause so called plateau potentials in medium spiny neurons of the striatum (and many other neurons). But what is the effect of co-activated clusters of spines more proximally in the dendrites where plateau potentials are not triggered? And how is dopamine modulation affecting the cell response to clustered activation?

Here we investigate these questions using a biophysically detailed model of a medium spiny neuron of the direct pathway. We specifically compare the somatic response of the cell to activation of clustered and non-clustered groups of dendritic spines as a function of mean somatic spine distance. Dopamine modulation is implemented as a set of changes to maximal conductances following a detailed literature study.

We see that clustered spines are most efficient in driving the cell if triggered in the medial part of the dendrite both in vitro and in vivo. We also see that dopamine modulation increases the influence of non-clustered input on the output of the cell relatively more than clustered.

We interpret these results as if dopamine can allow less well learned activation patterns to also drive the cell and thereby increase the variability of single neurons.

Our simulations are hence in line with experimental data showing that dopamine modulation can induce variability in striatal cell ensembles and connects this variability to spatial organization of spines.
Neuronal networks within the spinal cord coordinate rhythmic movements such as locomotion. The transcription factor DMRT3 is involved in the differentiation of the d16 class of spinal cord interneurons. A non-sense mutation in the horse Dmrt3 gene has major effects on gaiting ability, whereas mice lacking the Dmrt3 gene display impaired CPG activity and locomotion. Although the Dmrt3 gene is required for normal spinal neuronal network formation and function, a role for Dmrt3-derived neurons has not been demonstrated. Here we show that inhibitory Dmrt3 interneurons in mice receive extensive synaptic inputs from several sources, display accommodating properties, and are rhythmically active during fictive locomotion when they fire at frequencies independent to the ventral root output. Conditional removal of VIAAT dependent inhibitory neurotransmission from the Dmrt3 population resulted in a uncoordinated CPG output in vitro, severely impaired limb coordination in vivo, and increased limb synchrony at high running speeds. The present study provide novel insights on the role of Dmrt3 neurons in locomotor coordination and suggest that inhibition arising from Dmrt3 interneurons act to balance excitatory inputs, with subsequent impact on locomotor coordination.
The lateral pallium is the lamprey homologue of the mammalian cortex. It has a three-layered architecture with similar basic microcircuit components and intrinsic connectivity as the neocortex (Suryanarayana et al., 2016), as well as extrinsic projections targeting subcortical motor regions (Ocaña et al., 2015). We examine here the mapping of visual and olfactory inputs to pallium.

Primary retinal input, is relayed to pallium via thalamus. Extracellular multi-unit recordings showed that dorso-medial pallial neurons are activated by input from the retina. This region is distinct from the motor areas of pallium (Ocaña et al., 2015). The input shows a retinotopic organization with specific regions of this dorso-medial area responding to extracellular stimulations of specific quadrants of the retina - a visual pallium. Furthermore, GABAergic neurons maintain this retinotopy, since local injections of GABA antagonists remove the specificity.

Tracer injections revealed a reciprocal projection between pallium and thalamus. Dual tracer injections in pallium and pretectum/tectum revealed a dual labeled subpopulation of projection neurons in the retino-recipient region of thalamus, showing that visual information from thalamus is also relayed to pretectum/tectum.

We also show that input to pallial neurons from the olfactory bulb is relayed via two routes - directly and via a relay nucleus (dmtn), both of which terminate in distinct layers in the outermost molecular layer of pallium. Extracellular multi-unit recordings showed that large areas of pallium are activated from olfactory bulb inputs, overlapping with the motor areas.

This study is the first to examine how visual and olfactory inputs interact within the pallium.
Every day of our lives, our brains continuously plan and execute goal-directed actions, and without any effort we are aware of the actions of others around us. Action planning in the brain takes place between parietal and frontal motor cortices, and these same regions are believed to facilitate action understanding via "mirror" neurons, which are activated whether an action is performed or merely observed. The topic of mirror neurons has drawn considerable excitement and debate over the last two decades, and many fundamental questions remain unresolved, such as the biological basis of the mirror mechanism, the utility of mirror neurons to behavior, and the existence of mirror neurons in mammals other than primates. These and other issues stand to be resolved using lower model organisms, such as mice, for which powerful tools exist to perform anatomical and functional dissections at the circuit level. To this end, we are performing in vivo calcium imaging in layer 2/3 of the mouse posterior parietal cortex (PPC) while animals perform and observe goal-directed behaviors in a pellet-reaching task. We found that 40-50% of PPC neurons robustly and stably represented several behaviors, such as grasping for food, during performance of the task and, surprisingly, that a subset of cells showed tuning to the same behaviors during observation of a conspecific. Our results show for the first time neural correlates of observed behavior in the mouse cortex, and raise the possibility that the mouse could be used as a system to study sensory-motor "mirror" matching.
A complete transection of the spinal cord results in loss of postural functions, which do not recover over time. Instead, spastic, incorrectly-phased motor responses to postural sensory signals gradually develop.

The aim of the present study was to reveal these plastic changes, i.e., to characterize the activity of spinal postural networks at different time points after spinalization. For this purpose, rabbits in 3, 7, and 30 days after spinalization (at T12) were taken in acute experiments. After decerebration, stimulation was applied to hindlimbs which in preparations with intact spinal cord evoked postural limb reflexes (PLRs) constituting a substantial part of postural corrections in intact animals. During this stimulation putative spinal interneurons were recorded extracellularly in L5. The data were compared with those obtained in control and in rabbits after acute spinalization.

As in control, at each time point after spinalization, neurons responding to PLRs-related limb stimulation were found. Their characteristics of activity (which exhibited a significant decrease after acute spinalization as compared to control) reached the control value already in 3 days after spinalization. At this moment, motor responses to PLRs-related limb stimulation were practically absent. This result suggests that there are two processes of plastic changes in the postural networks, which are triggered by spinalization – a slow process of recovery of the motoneuronal excitability (taking months), and a rapid process of restoration of the normal activity level in spinal interneurons (taking days). In addition, a dramatic increase in the relative number of neurons activated from skin receptors was observed.

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Key words: postural limb reflexes, spinal cord injury, rabbit, spinal interneurons.
The brainstem preBötzinger complex (preBötC) generates the rhythm for inspiratory breathing movements, and can remain rhythmically active in vitro—both in acute brainstem slices and organotypic cultures. The onset of neural activity during the inspiratory phase of the respiratory cycle (i.e. preinspiratory activity) develops into inspiratory-related motor output, and may depend on the activity of neurons in the preBötC that exhibit a transient outward K+ current, IA. We took advantage of enhanced imaging conditions inherent to organotypic slice cultures (i.e. flattened tissue, reduced light scattering) in order to measure the impact of dendritic IA on Ca2+ transients evoked by voltage increases propagating through the dendrites of preBötC neurons. We observed a significant increase in the amplitude of stimulus-evoked transients in dendrites of rhythmically active preBötC neurons after 4-aminopyridine (4-AP) was applied either to the perfusion bath or to local dendritic regions. We conclude that an IA is present on dendrites of preBötzinger neurons, and propose that IA acts as a dendritic filter on synaptic input, shunting sparse input while enabling strong excitatory events to pass when the current is steady-state inactivated. Filtering caused by IA on dendrites may allow preBötC neurons to distinguish sparse input characteristic of quiescent network states (e.g., post-inspiratory or expiratory phases) from synaptic input received during heightened activity states (e.g. recurrent excitation during the build-up to inspiratory bursts). Dendritic IA in rhythmically active preBötC neurons would thus ensure that excitatory synaptic drive is synchronized and well-coordinated among network constituents during the onset of inspiratory motor activity.
Prostaglandins play a pivotal role in the regulation of pain, inflammation, and fever. The most abundant prostaglandin in the body, the prostaglandin E₂ (PGE₂), exerts its functions by binding to specific G protein-coupled receptors, namely EP₁, EP₂, EP₃ and EP₄. The prostanoid system has been only partially explored in the brain. The locus coeruleus (LC), the main noradrenergic nucleus in the central nervous system, expresses EP₂, EP₃ and EP₄ receptors. The aim of our research was to functionally characterize the EP₃ receptor by single-unit extracellular electrophysiological recordings in rat brain slices containing the LC. Administration of increasing concentrations of the endogenous PGE₂ (0.3 nM-1.28 µM), the selective EP₃ receptor agonist sulprostone (0.3-80 nM) and the PGE₁ analogue misoprostol (0.3-320 nM) induced concentration-dependent decreases of the neuronal firing rate of LC cells. The inhibitory effects of these agonists on the neuronal activity were blocked by the selective EP₃ receptor antagonist L-798106 (10 µM), which caused rightward shifts in the concentration-effect curves for PGE₂, sulprostone and misoprostol. However, the EP₂ receptor antagonist PF-04418948 (10 µM) or the EP₄ receptor antagonist L-161982 (10 µM) failed to shift concentration-effect curves for the agonists. Moreover, inactivation of Gᵢ/o-proteins by overnight perfusion with pertussis toxin significantly reduced the sulprostone-induced inhibition of the neuronal activity of LC cells. In conclusion, LC neurons may be regulated by the PGE₂ system in an inhibitory manner through somatodendritic Gᵢ/o-protein-coupled EP₃ receptors.
Prostaglandins are linked to inflammation and fever, but they have also been described to alter the activity of the main respiratory rhythm generator the pre-Bötzinger Complex (preBötC). This may lead to life-threatening events, especially in newborn babies. In the preBötC, prostaglandin E₂ (PGE₂) depresses the respiratory activity in an EP3 receptor-dependent manner through activation of Gᵢ-protein signaling pathways. Additionally, opioids depress respiratory activity through actions on μ-opioid receptors in the preBötC. However, the respiratory depressive effect of opioids during inflammatory states, e.g. during infections and surgery, and the possible interactions has not been fully elucidated. Therefore, we explore the mechanisms underlying the respiratory depression induced by the opioid in relation to the prostanoid system. We performed live time-lapse calcium imaging on organotypic brainstem slices of both wild type and mice lacking the EP3 receptor. Administration of increasing concentrations of PGE₂ (10⁻³ – 100 nM) and the μ-opioid receptor agonist DAMGO (0.5 – 5 µM) revealed an inhibitory effect on the network frequency. Ongoing experiments investigate whether synergistic or competitive effects are present and what signaling pathways are activated. This could identify new therapeutic targets for alleviating opioid-induced respiratory depression and improve analgesic treatment regimens.
In reinforcement learning, contiguity entails not just the temporal proximity between the environmental stimuli and reinforcement signal but also the temporal order of the inputs. This sequence-dependent eligibility trace-like temporal rule appears to be true for even subcellular signal integration. Specifically, the integration of calcium and dopamine at the striatal medium spiny neurons (MSNs) lead to an increase in synaptic strength in a Ca\(^{2+}\)-Calmodulin-dependent kinase II (CaMKII) dependent fashion. However, to elicit the CaMKII dependent response it is crucial that dopamine follows, and not precedes, the calcium input within a short interval. Despite its apparent relevance, the subcellular mechanism responsible for imposing these constraints remains unclear. In this modeling study, we put forth a mechanism which could explain these observations. This mechanism relies on the coordinated activity of two striatally enriched phosphoproteins, DARPP-32 and ARPP-21. Each of them implements different aspects of the temporal constrains. DARPP-32 is responsible for enforcing the constraint of temporal proximity on the calcium-dopamine integration whereas ARPP-21 implements the input-order constraint. Furthermore, the inherent Ca\(^{2+}\)/Calmodulin sequestering property of ARPP-21 could also lead to an inter-trial refractoriness in a multi-trial conditioning scenario. Our results highlight the possible role of phosphoproteins in the temporal aspects of striatal signal transduction.
Peroxisome proliferator-activated receptor-γ (PPARγ) is a transcription factor that belongs to the nuclear receptor superfamily and it modulates the expression of genes involved in adipogenesis, glucose metabolism and inflammatory responses. PGC-1α is a PPARγ coactivator 1α that regulates mitochondrial biogenesis and energy metabolism. Our data have shown that overexpression of PGC-1α in brain in transgenic mice influence neuronal viability and gene expression as well as mitochondrial oxidative phosphorylation. In search of genes regulated by the PGC-1α/PPARγ axis we have performed a transcriptome analysis and identified key targets for PGC-1α action in brain. Among these are GABA receptors especially GABARα2 that is involved in regulating affective and other types of behavior in experimental animals. We further showed that the compound pioglitazone activating PPARγ also increases GABARα2 expression in vivo and in vitro. Pioglitazone is a drug used in the clinics for treatment of type 2 diabetes suggesting that the drug can influence the GABAergic system in the brain. We are currently studying the relevance of the link between PGC-1α/PPARγ and GABA receptors in more detail using different culture and animal models.
(Arc) is implicated as a master regulator of long-term synaptic plasticity and memory formation in mammalian brain. Arc acts at synapses and within the nucleus, but the mechanisms controlling Arc localization and function are little known. As Arc transcription and translation are regulated by ERK signalling, we asked whether Arc protein itself is phosphorylated by ERK. GST-fused Arc of rat origin was able to pull down endogenous ERK2 from rat hippocampal lysates. Using a peptide array, we show that ERK binds a non-canonical docking (D) motif in the C-terminal domain of Arc, and this interaction is abolished by phosphorylation of Tyr309. Activated ERK2 phosphorylated bacterially expressed Arc in vitro at all five predicted sites, as confirmed by phospho-specific protein staining and LC-MS/MS analysis. In neuroblastoma cells expressing epitope tagged-Arc, we demonstrate ERK-dependent phosphorylation of Arc in response to activation of muscarinic cholinergic receptors with carbachol. Using phosphosite-specific antibodies, this stimulus-evoked phosphorylation was shown to occur on Ser206 located within the central hinge region of Arc. Furthermore, Ser206 phosphorylation of endogenous Arc was detected after induction of long-term potentiation (LTP) in the perforant path input to the dentate gyrus of live rats. In cultured hippocampal neurons expressing phosphomutant Arc under control of the activity-dependent promoter, we show that Ser206 phosphorylation regulates the nuclear:cytosolic localization Arc. Thus, the neuronal activity-induced phosphomimic exhibits enhanced cytosolic localization relative to phosphodeficient and wild-type Arc. Taken together, this work demonstrates stimulus-evoked ERK-dependent phosphorylation and regulation of Arc protein.
**Background:** Infectious periods in newborn babies may induce respiratory dysfunction through the action of prostaglandin E2 (PGE2). We recently discovered that PGE2 decrease the activity of the preBötzinger Complex, the main respiratory central pattern generator in the brainstem. PGE2 also increased the activity of the chemosensitive parafacial respiratory group (pFRG), and was released during hypercapnic challenge. We hypothesized that astrocytes are the source of PGE2.

**Methods:** We investigated the role of astrocytes in respiration using chemogenetics, using mice with astrocytes that through induced expression of GFP and the Gq-coupled MrgA1 receptor were identifiable and possible to activate. The respiratory networks were studied with calcium time-lapse imaging in organotypic brainstem slice cultures.

**Results:** We report the presence of two distinct subtypes of astrocytes. Most astrocytes were dormant, showing no rhythmic calcium oscillations. However, a subgroup of active astrocytes displayed rhythmic calcium oscillations, similar to respiratory neurons. The proportion of active astrocytes and neurons differed between the two respiratory regions. Further, the active astrocytes formed a subnetwork within the respiratory network, distinct from the neuronal. Activation of the MrgA1 receptor tripled the oscillation frequency of the active astrocytes in both regions. However, the neuronal activity in the preBötzinger complex was not altered. In contrast, pFRG neurons increased their activity after astrocyte activation. Astrocyte activation of the pFRG also triggered a release of PGE2 and blunted the hypercapnic response.

**Conclusion:** Astrocytes play an important, active role in the respiratory networks and modify respiratory activity in response to hypercapnia through the release of PGE2.
Recently generated Tph2 knockout mice provide a model to investigate the effect of serotonin depletion on the development of behavior and its underlying neural substrates. In these mice, serotonergic neurons are generated but fail to synthesize serotonin. Here we have focused on the effects of Tph2 knockout on locomotion, assessed both behaviorally and electrophysiologically in isolated spinal cord preparations.

Behavioral tests during the first 2 postnatal weeks revealed several motor deficits in Tph2-/- mice compared to Tph2+/-/ and Tph2+/+ mice, including an asymmetric walking pattern with misalignment of the hindpaws and altered hindlimb extension and a larger number of failures in left/right and flexor/extensor alternations during swimming. Neonatal Tph2-/- mice also exhibited a substantially diminished vestibulospinal reflex triggered by axial rotation.

To assess whether these behavioral deficits might be due to alterations in central locomotor circuitry, we analyzed neurochemical (NMDA+dopamine+serotonin)-induced fictive locomotion in neonatal mice by recording from L2-L5 ventral roots. There were significant differences in cross-correlation coefficient and phase relationships in Tph2-/- versus Tph2+/+ mice. The range of frequencies exhibited was narrower in Tph2-/- mice with a main peak of about 0.1 Hz, whereas in Tph2+/+ mice the range was 0.1-0.3 Hz.

Modifying the neurochemical cocktail indicated that serotonin was involved in eliciting activity in Tph2-/- spinal cords. We conclude therefore that serotonin receptors continue to be expressed by neurons in spinal motor circuits, but that the absence of serotonin in serotonergic synapses during development impacts on the connectivity and/or functional expression of the locomotor central pattern generator.
Axon-glial communication is a known modulator of cellular functions. In the peripheral nervous system (PNS), Schwann cells (SCs) express a variety of receptors for neurotransmitters, which potentially enable them to detect axonal activity. We previously demonstrated that SCs also express monocarboxylate transporters (MCTs) that allow the import/export of lactate and pyruvate, that are important high-energy substrates. We hypothesize that SCs may be able to respond to axonal cues by releasing these substrates which can then be used as “on demand” energy source by the axon. To test this hypothesis, we use primary rat Schwann cells exposed to various neurotransmitters and we evaluate their response via characterization of multiple intracellular signaling cascades. In parallel, we are establishing in vivo models to study the physiological role of MCTs in SCs. We anticipate that the generated data will provide insight into the importance of the axonal and glial metabolic interplay for maintenance of the PNS integrity and may provide new ideas for therapeutic strategies for neurodegenerative diseases.
In the nervous system, four calcium/calcineurin-regulated members of the nuclear factor of activated T-cells (NFAT) family of transcription factors, NFATc1-c4, are involved in many developmental and functional processes, such as corticogenesis, synaptogenesis, synaptic plasticity and neurotransmission, that all need precise gene regulation. Therefore it is important to understand molecular events that contribute to the regulation of the transcriptional activity of specific NFAT isoforms. Previously, we have shown that there are a number of alternative splice variants of NFAT genes expressed in the brain and that neuronal activity leads to isoform-specific transactivation capacities of different human NFAT proteins. Here we looked at the effect of sumoylation as a possible regulator of the transcriptional activity of different human NFAT isoforms in response to membrane depolarization and compared the results to those obtained from non-neuronal HEK293-FT and BHK-21 cells in response to calcium signaling. Our results show that in primary hippocampal neurons, sumoylation represses the transcriptional activity of NFATc1, NFATc2, and NFATc3 isoforms, whereas in cortical neurons, transactivation capacity of only NFATc1 and NFATc2 is repressed by sumoylation. In non-neuronal cells, however, transcriptional activity of all four NFAT isoforms is repressed by sumoylation in HEK293-FT cells, while only NFATc1 and NFATc2 isoforms are affected by sumoylation in BHK-21 cells. Altogether, our results show that sumoylation represses the transcription activation capacities of NFAT isoforms and that the effect is cell type-specific.
Cortical interneurons undergo extensive synaptogenesis and maturation of intrinsic properties during the first weeks after birth. In particular, parvalbumin (PV)-expressing interneurons go through a shift in their transcriptional profile during the second postnatal week, believed to be indispensable for their maturation. Because Sox6 is expressed in these cells throughout postnatal maturation, we investigated its role on late maturation and synaptic function and maintenance. For this, we utilized a conditional knockout strategy to specifically remove Sox6 in interneurons at different postnatal stages. Our results show that Sox6 was necessary for discrete aspects of cortical PV interneuron maturation independently of when it was removed (P7 or P21). By removing Sox6, although PV-expression was normal and their electrical properties mature, we observed a 30% decrease of PV-cells enwrapped by perineuronal nets (a hallmark for functional maturation). More strikingly, loss of Sox6 in individual PV-cells (in otherwise wild type tissue) led to a robust decrease of size of PV interneuron axonal boutons contacting pyramidal neuron cell bodies, suggesting it to be a cell-autonomous effect. Furthermore, PV-cells lacking Sox6 displayed reduced TrkB-FL expression, which, when overexpressed in PV-cells lacking Sox6, was sufficient to rescue the axonal phenotype. Preliminary paired recordings of PV-cells and pyramidal neurons suggest that the decrease in bouton size leads to higher failure rate. We are currently investigating if this role of Sox6 in PV-cells persists till adulthood.
L-Glutamate is the major excitatory neurotransmitter in the mammalian brain and the synaptic glutamate transmission is highly regulated. The importance of a balanced glutamate transmission is underscored by the fact that alterations in the glutamatergic transmission has been demonstrated in the pathophysiology of several neurological disorders ranging from epilepsy to depression and neurodegenerative diseases. Astrocytes play an active role in maintaining synaptic control through glutamate uptake from the synaptic cleft by glutamate transporters; however, how this uptake is regulated is far from understood.

In this study we use rat hippocampal slices to measure the contribution of the astrocytic glutamate transporters in glutamate clearance by recording extracellular glutamate as well as directly measuring the current generated by the glutamate transporter. Synaptic release of glutamate was evoked by electrical stimulation delivered with a bipolar electrode placed in Schaffer collaterals. L-Glutamate was recorded using enzyme-based microelectrodes coupled to a FAST-16 mkII electrochemical recording system and the contribution of EAATs was determined by using the blocker DL-TBOA. Secondly we performed whole cell patch clamp recordings of astrocytes in the striatum radiatum and measured the astrocytic glutamate transporter current in response to different stimulation intensities of the Schaffer collaterals. The astrocytic glutamate transporter current was isolated using Picrotoxin, DL-AP5 and NBQX.

We saw a proportional increase in the levels of L-Glutamate and the glutamate transporter current in response to different intensities of stimulation. We will use these approaches to study the astrocytic regulation of the glutamatergic system in rat models of psychiatric and neurodegenerative diseases.
HCN channels are important for regulation of distal dendritic signaling and synaptic integration in pyramidal neurons, and are modulated by several transmitters. We investigated effects of adrenergic $\alpha_2$ and $\beta$-receptor agonists in rat hippocampal CA1 pyramidal neurons.

We found previously that $\alpha_2$-receptor agonists via cyclic AMP directly upregulate HCN channels (h-current) in CA1 neurons, independently of cAMP-dependent protein kinase A (Pedrazani and Storm, 1995, PNAS 92: p.11716-720).

The $\alpha_2$-receptor agonists clonidine (10 µM) strongly reduced the typical, HCN channel-mediated sag in response to 500 ms long hyperpolarizing current pulses, and increased the input resistance. These effects were mimicked and occluded by the HCN channel-blocker ZD7288 (10 µM), suggesting an $\alpha_2$-adrenergic downregulation of HCN channel activity, similar to what has been reported in other neuron types. In parallel, clonidine (10 µM) strongly reduced the peak amplitudes of a summed series of evoked excitatory synaptic potentials (EPSPs), although a closure of HCN channel would be expected to enhance EPSP summation and reduce electrotropic attenuation. However, the effect of clonidine on EPSPs was accompanied by an increase in paired-pulse facilitation, and was not occluded by ZD7288, suggesting that it was mediated by a presynaptic inhibition of glutamate transmission.

These results suggest that two opposite types of adrenergic modulation of HCN channels coexist in CA1 hippocampal pyramidal neurons: HCN channels activity is suppressed via $\alpha_2$-receptors, while being enhanced via $\beta$-receptors and cyclic AMP. These may provide specific mechanisms for diverse and subtle regulation of distal dendritic signaling and synaptic integration in pyramidal neurons.
The brain lacks lymphatic vessels and waste products are cleared along paravascular pathways, termed the "glymphatic system". Glymphatic waste clearance is dependent on glial water channels and is twice as efficient during sleep than in the awake state. However, the precise mechanisms that orchestrate brain waste clearance are still not known. We hypothesize that astrocytic calcium signaling differs during wakefulness and sleep and potentially regulates the glymphatic fluid flow. We use two-photon microscopy combined with chronic windows and viral injection of genetically encoded calcium sensors (GECIs) to thoroughly characterize astrocytic calcium signals in the cortex of sleeping or awake mice. Preliminary data indicate that astrocytic calcium signaling is suppressed during sleep. Resolving the mechanisms involved in brain waste removal is important for our understanding of a number of neurodegenerative disorders, including dementia and Alzheimer's, and may pave the way for new treatment strategies.
Physical exercise can improve brain function and delay neurodegeneration, but the initial signal from muscle to brain is unknown. Here we show that the lactate receptor (HCAR1) is highly enriched in fibroblast-like cells that line and surround the pial blood vessels supplying the brain, and that activation of HCAR1 stimulates vascular endothelial growth factor A (VEGFA) levels and angiogenesis in hippocampus. High intensity interval exercise (five days weekly for seven weeks), as well as L-lactate injected subcutaneously to similarly increase blood lactate levels, caused a substantial increase in brain VEGFA protein and microvessel density in wild-type mice, but not in knockout mice lacking HCAR1. In contrast, skeletal muscle showed no vascular HCAR1 expression and no HCAR1 dependent change in vascularization induced by exercise or lactate. To our knowledge, this is the first demonstration that a substance released by exercising skeletal muscle induces supportive effects in brain through an identified receptor.
Short-term synaptic plasticity (STP) refers to an increase (facilitation) or decrease (depression) in the synaptic efficacy depending on the recent history of presynaptic spiking activity.

Using numerical simulations, we investigate how STP imposes constrains on distribution of spiking activity over a group of presynaptic neurons to maximize the information transmission. To this end, we searched for how extra firing rate (occurring in a small time window) carrying an information should be distributed over the population of presynaptic neurons in order to maximize the Proportion of Released Resources (PRR). We found that for a fixed input firing rate, PRR changed in a non-monotonic fashion as a function of number of recruited presynaptic neurons. Furthermore, the number of input neurons required to maximize PRR increased linearly as a function of the extra input rate. Finally, PRR was maximized for a fewer number of presynaptic neurons when synapses exhibited short-term-facilitation as compared to when synapses exhibited short-term-depression.

Our analysis predicts that in brain areas where population code is confined to few high firing rate neurons, excitatory synapses should predominantly show short-term-facilitation and vice versa for more distributed inputs. In summary we show that there is a close relationship between sparsity of representation in population coding and STP features, suggesting that synaptic STP could work as a spatial filter, endowing the postsynaptic target of an ensemble with the ability to differentiate spatially structured information from noise.
The distinctive properties of reactive astrocytes and the consequence of astrogliosis for brain function still remain a matter of debate. Despite the fact that “reactive” astrocytes are part of the pathophysiology of many psychiatric and neurodegenerative disorders, a clear definition defining reactive astrocytes, molecularly and functionally, is lacking. Our laboratory has established immunohistochemical protocols using Glial fibrillary acidic protein (GFAP) and Calcium-binding protein S100β as astrocytic markers in order to examine morphology and protein expression in reactive astrocytosis. Previous research has demonstrated that reactive astrocytosis influences synaptic function, and we focus on two potentially relevant changes in reactive astrocytes: synthesis of the inhibitory neurotransmitter Gamma-amino butyric acid (GABA) and decreased expression of the excitatory amino acid transporter (EAAT) that regulates glutamate uptake at the synapse. By examining GABA/S100β as well as EAAT-1/GFAP ratio, we are able to investigate in which ways inflammatory processes modify astrocyte morphology and contribute to altered expression of GABA and EAAT-1 in astrocytes. Using a variety of co-localization methods including Intensity Correlation Analysis as well as Mander’s and Pearson’s coefficients, we are capable to reliably and objectively quantify and compare astrocytic GABA and EAAT-1 levels in different rat models of neuroinflammation and psychiatric disorders.
Fine-tuning of excitatory transmission in the brain can be achieved by allosteric modulation. Positive allosteric modulators (PAMs) of AMPA receptors have been shown to improve memory, facilitate synaptic transmission, promote synaptic plasticity and increase BDNF levels. Conversely, there is a risk of tipping the delicate excitatory-inhibitory balance. We have recently documented that SorCS3 (sortilin-related receptor CNS expressed 3) deficient synapses display impaired synaptic transmission and plasticity [1, 2]. Consequently, we hypothesized that PAMs may improve SorCS3-deficient synapses.

Here we employed a novel subunit-bridging PAM entitled phenyl-1,4-bis-alkylsulfonamide (CMPDA) [3]. To analyze the modulator in native synapses, we prepared acute brain slices from the SorCS3-deficient mouse model [1]. Field excitatory postsynaptic potentials (fEPSPs) were recorded and CMPDA was applied by bath perfusion.

Interestingly, 0.1 µM CMPDA rescued a weak long-term potentiation (LTP) protocol more profoundly in knockout, and even promoted a strong LTP protocol. 0.1 µM potentiated fEPSP slopes about 1.9-fold in wild-type and 1.7-fold in knockout. 1 µM potentiated fEPSP slopes about 3-fold in wild-type and 4.5-fold in knockout. Paired stimulations revealed that 1 µM reduced paired-pulse facilitation at all intervals, while 0.1 µM increased the facilitation selectively at 50 ms, and only in knockout. Intriguingly, 3 µM produced pronounced pathological epileptiform activity, revealing repeated pyramidal cell firing, even upon single stimulations.

In summary, CMPDA positively affects synaptic impairments in SorCS3 knockouts, but triggers epileptiform activity, even at relatively low concentrations.

Striatum is a network of inhibitory medium spiny neurons (MSNs) receiving excitatory cortical and thalamic input and playing a crucial role in motor and cognitive functions. Striatal MSNs express D1 or D2 dopamine receptors and form a two-population mutually inhibitory network, and in animal models under ketamine anesthesia exhibit transitions between depolarized (up-states) and hyperpolarized (down-states) membrane potentials. To understand the role of striatum in brain function and dysfunction it is important to characterize the differences in the integrative properties of the two type of MSNs, and in the cortical and thalamic inputs to them.

Here we use the statistical properties of the up- and down-states of the D1 and D2 MSNs to estimate relative differences in the input to these neurons. From the spectra of membrane potentials, we estimated that the effective membrane time constant (τ_{eff}) in down-states is on average 1.72 times larger than in up-states, suggesting that MSNs in up-states operate in a synaptically driven high-conductance regime. Furthermore, by comparing D1- and D2-MSN statistics and spike-triggered-averages, we found that D1-MSNs on average receive stronger excitatory inputs than D2-MSNs. Additional statistical analysis, as well as theoretical modeling, point to the conclusion that the excitatory input to MSNs is correlated.

In summary, by analyzing in vivo recorded data we show that MSNs operate in a high-conductance regime, and that D1 cells receive either stronger or more excitatory input than D2 MSNs. Furthermore, our simulations show evidence that this input is correlated.
Oriens lacunosum-moleculare (OLM) and Martinotti cells are interneurons which form GABAergic synapses onto the distal apical dendrites of pyramidal neurons in the hippocampus and the cortex, respectively. The activity of these cells and their responses to neuromodulatory drive is crucial for understanding how local activity in hippocampal and cortical circuits affects the processing of incoming distal signals.

We investigated the effect of muscarinic acetylcholine (mAChR) and metabotropic glutamate receptor (mGluR) activation on OLM and Martinotti cells as identified by a specific genetically encoded marker.

Despite analogous location, morphology and functional integration in their respective circuits, these cells responded very differently to mAChR and mGluR agonists.

In OLM cells agonists at both receptors induced large plateau potentials, seen as sustained depolarizations triggering action potential firing following the offset of an excitatory stimulus. Plateau potentials have been observed in a variety of cell types and have been implicated in mechanism of memory.

Furthermore, during combined activation of mAChRs and mGluRs with low agonist concentrations, we observed the emergence of plateau potentials of amplitude greater than expected from the amplitude in the presence of either agonist individually, indicating synergy between the mAChR and mGluR signaling pathways.

These results suggest intracellular pathways can integrate signaling from separate neurotransmitter systems to generate heightened activity in cells essential for information routing in the hippocampus.

It also shows that cells related by function, morphology and gene expression, can express different behaviour in response to neuromodulation and are therefore likely to play differing roles during different brain states.
C23: Hydrogen sulfide plays an anti-inflammatory role during systemic inflammation up-regulating hypothalamus p-Akt and plasma IL-4

Presenter: Rodrigo Restrepo Fernández - University of Sao Paulo
Theme: Neural Excitability, Synapses, and Glia
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The gaseous messenger hydrogen sulfide (H₂S) modulates endotoxin-induced systemic inflammation, acting as a cryogenic molecule in rats, although the underlying mechanisms are still poorly understood. Since endotoxin is a Toll-like receptor 4 (TLR4) ligand and recent evidence indicates there is a possible a cross-talk between the TLR and phospho-Akt (p-Akt) signaling pathway, the current study was aimed to investigate whether H₂S acts as an anti-inflammatory mediator through the activation of Akt in the the anteroventral preoptic region of the hypothalamus (AVPO), during systemic inflammation. The enzyme cystathionine β-synthase (CBS – responsible for H₂S endogenous production in the brain) was inhibited using aminoxyacetate (AOA; 100 pmol, icv) combined or not with endotoxin administration (LPS; 2.5 mg/kg, ip). To investigate the mechanisms responsible for the immune response adjustments, CBS and p-Akt expression profiles were verified, along with plasma cytokines (IL-1β, IL-6, IL-10, TNFα, IFN-γ, and IL-4). Endotoxin caused typical hypothermia followed by fever. During the febrile phase CBS relative expression was significantly decreased whereas p-Akt was significantly increased when compared to both euthermic and hypothermic rats. CBS inhibition attenuated hypothermia and increased fever, besides abolishing endotoxin-induced increase in Akt activity. Plasma cytokines tented to increase during systemic inflammation, but only IL-4 showed a similar pattern in relation to Akt. These data are consistent with the notion that during the course of fever, the gaseous messenger H₂S production is inhibited, potentiating hypothermia and inhibiting fever. This anti-inflammatory role during systemic inflammation involves a H₂S-induced up-modulation of Akt and plasma IL-4.
The human cortex comprises mature neurons, which are functional interconnected and is able to generate synchronous activity. Human induced pluripotent stem cell (hiPSC)-derived neural stem cells recapitulate processes of corticogenesis in vitro, e.g. time-dependent sequential production of cortical neurons, cortical layer development, neuron to glial transition. The electrophysiological maturation on single and network level of hiPSC-derived cortical neurons are considered as a process which required several weeks up to months, and depend on co-culturing with astrocytes obtain from primary rat or human fetal cell cultures.

Here, we show a procedure to generate hiPSC-derived cortical aggregates comprising of neurons and astrocytes obtained from the same human individual. In detail, confocal laser microscopy revealed that hiPSC-derived cortical aggregates comprise of early and late-born cortical neurons, S100-positive astrocytes, vGlut1 and PSD-95 mature synapse. Cell-attached and whole-cell recordings demonstrated that neurons within hiPSC-derived cortical aggregates show mature electrophysiological properties, i.e. generation of spontaneous action potentials, bursts as well as inhibitory and excitatory spontaneous synaptic activity. MEA recordings detected synchronize cortical network activity within 3 weeks of cultivation.

The here presented fast procedure of neural differentiation of hiPSC combined with the MEA technology allows to reveal direct function of neurons at the neuronal network level, paving the way for personalised and patient-specific preclinical studies for pharmacological testing of neuroactive drugs.
Glucagon-like peptide-1 (GLP-1) is a metabolic hormone originated mostly from intestine and stimulates insulin secretion from pancreatic islet beta cells in a glucose-dependent manner. Not only peripheral tissues but also many brain regions including the hippocampus express GLP-1 receptors. The hippocampus is a center for memory and learning. Previously we have shown that GLP-1 and its analogue exendin-4 modulate gamma-aminobutyric acid (GABA) signaling in the rat hippocampal CA3 pyramidal neurons (Korol et al, 2015a). In addition, we have studied how diazepam, the positive allosteric modulator of the GABA_A receptors, together with exendin-4, as well as liraglutide, GLP-1 analogue, affected GABA_A receptor-mediated synaptic and tonic currents in CA3 neurons under the study. Whole-cell patch-clamp method was applied to hippocampal slices from 16–20 days old Wistar rats to register GABA_A receptor-mediated currents in the CA3 pyramidal cells. GLP-1 and exendin-4 transiently increased the frequency and amplitudes of the spontaneous inhibitory postsynaptic currents (sIPSCs) as well as enhanced the GABA_A receptor-mediated tonic current. Diazepam caused increase in amplitudes and frequency of the sIPSCs and persistent potentiation of GABA_A receptor-mediated tonic current (Korol et al, 2015b). Liraglutide modulated GABA signaling predominantly by presynaptic mechanism. The data show that GLP-1 and exendin-4 enhance sIPSCs and subpopulation of extrasynaptic GABA_A receptors and their effect is somewhat different from that of liraglutide in hippocampal CA3 pyramidal neurons. These results further support that metabolic hormones and their analogues impact hippocampal function.

References


Synaptic plasticity is the ability of synapses to change in strength in response to use or disuse. Long-term potentiation (LTP) is a cellular mechanism responsible for strengthening a synapse. LTP in the hippocampus is studied for understanding, formation of memory. LTP is achieved through brief, high-frequency stimulation (HFS) of medial perforant input from the entorhinal cortex. HFS leads to induction of activity-regulated cytoskeleton-associated protein (Arc). Arc expression is rapid and required for consolidation of LTP and other forms of synaptic plasticity. Arc is capable of binding diverse protein partners in distinct neuronal subcompartments. However, little is known about protein-protein interactions generated by newly synthesized Arc protein in LTP.

In Arc TimeSTAMP knockin mice, the Arc protein is fused to a self-cleaving viral protease followed by two HA epitope tags. The systems allows drug-dependent epitope tagging of newly synthesized Arc protein. In the absence of the protease inhibitor drug (BILN 2061), the protease is active and the Arc protein is left untagged. In the presence of BILN, protease activity is inhibited and the HA-tag is retained on new copies of Arc. Immunohistochemistry can be used to localize new copies of Arc and total Arc (pre-existing and new). In addition, HA-immunoprecipitation can be used to isolate protein interaction complexes formed by newly synthesized Arc.

This technology has the potential to capture the dynamic functions of newly synthesized Arc in synaptic plasticity and behavior.
During the past few years, microglia has generated a lot of interest since it has been shown that they influence neuronal development and synaptic function. The intercellular adhesion molecule-5 (ICAM-5) expressed by neurons is also involved in these processes. Interestingly, NMDA receptor activation causes proteolytic shedding of the ICAM-5 ectodomain, allowing spine maturation to proceed (Please see the review about ICAM-5 by C.G. Gahmberg in Cell Adhesion Molecules: Implications in Neurological Diseases, Springer, 2014, for further information). Previous studies have focused on the ICAM-5 interaction with integrin receptors on T-cells and neurons. Since microglia also express integrins, we investigated the possible regulatory role of ICAM-5 on microglia. Integrin binding to ICAM-5 was identified in a phage display technique, among other interesting and novel binding partners. Adhesion- and immunofluorescence assays confirmed the involvement of beta 1 and beta 2 integrin on microglia in the binding to ICAM-5. On-going investigations are assessing the molecules involved in the morphological and functional changes ICAM-5 induces in microglia in vitro. It will be very interesting to study the in vivo interaction of microglia and neurons in our ICAM-5 knock out mouse line in the future.
Arc protein is implicated as a master regulator of long-term forms of synaptic plasticity and memory formation, but the mechanisms controlling Arc protein function are little known. Post-translation modification by small ubiquitin-like modifier (SUMO) proteins has emerged as a major mechanism for regulating protein-protein interactions and function. We first show in cell lines that ectopically expressed Arc undergoes mono-SUMOylation. The covalent addition of a single SUMO1 protein was confirmed by in vitro SUMOylation of immunoprecipitated Arc. To explore regulation of endogenous Arc during synaptic plasticity, we induced long-term potentiation (LTP) in the dentate gyrus of live anesthetized rats. Dentate gyrus LTP consolidation requires a period of sustained Arc synthesis driven by brain-derived neurotrophic factor (BDNF) signaling. Using coimmunoprecipitation of native proteins, we show that Arc synthesized during the maintenance phase of LTP undergoes mono-SUMO1ylation. Local infusion of the BDNF scavenger, TrkB-Fc, during the maintenance phase of LTP resulted in rapid reversion of LTP, inhibition of Arc synthesis, and loss of SUMO1ylated Arc. Subcellular fractionation showed that SUMOylated Arc is expressed in the dentate cytoskeletal fraction under basal conditions. Following LTP induction, levels of unmodified Arc increase in multiple subcellular fractions (cytosol, membrane, nuclear, and cytoskeletal), whereas enhanced expression of SUMOylated Arc was specific to the cytoskeletal fraction. Coimmunoprecipitation analysis further showed that SUMO1ylated Arc forms a complex with the F-actin binding protein drebrin A, a major regulator of actin cytoskeletal dynamics in dendritic spines. Although Arc interacted with a functionally diverse set of proteins (dynamin 2, CaMKIIβ
Longterm cognitive impairment after peripheral surgery or trauma is a common and serious complication particularly in the elderly population. While there are growing body of evidence that surgery-induced inflammation play a key role behind this surgical phenotype, the pathogenesis within the central nervous system is not fully understood.

In animal models, surgery is associated with brain immune activation with later cognitive impairment (Terrando et al., 2011). To further understand the temporal pattern of immune activation and simultaneous changes in hippocampal synaptic transmission we here investigated the neuronal-glial function combining astrocyte calcium imaging and whole-cell patch clamp in CA1-pyramidal cells with molecular tools.

We found a down-regulation in the mRNA of the astrocyte marker GFAP and aquaporine-4 at 24h and 72h post-trauma that was accompanied with loss of Ca$^{2+}$ signaling at 24h, without impact on the neuronal function. However, at 72h post-trauma the frequency and amplitude of the excitatory post-synaptic currents from CA1-pyramidal cells were increased vs. naïve-mice. Likewise, synaptic protein levels and astrocyte glutamate transporters were also affected at 72h. Notably, lactate that is mainly produced by astrocytes and an essential energy substrate for memory formation, decreased early in a temporal manner after surgery, i.e. 6h and 72h.

These findings confirm an active crosstalk between the peripheral immune system and the brain after surgery, and furthermore suggest a critical role for astrocytes that precede changes in neuronal activity and later cognitive impairment. Hippocampal lactate fluctuations highlights an aberrant astrocyte/neuronal metabolic coupling that potentially may underlie cognitive dysfunction in this model.
The pancreatic islet hormone insulin, in addition to its critical role in blood glucose regulation, has actions in brain modulating neuronal function. GABA (gamma-aminobutyric acid) regulates neuronal excitability and network activity by activating GABA_\text{A} receptors that evoke phasic and tonic inhibitory conductance. The hippocampus has distinct sub-domains along the longitudinal axis that are involved in learning, memory, emotion and metabolic control. We study the insulin effects on GABA_\text{A} receptors-mediated currents in rat and mouse hippocampus.

Quantitative RT-PCR, immunochemistry, for identifying the insulin receptor, and electrophysiological recordings were performed on rodent hippocampal slices. Our results show that the insulin receptor's mRNAs and proteins are differentially expressed in hippocampal sub-domains. Insulin incubation enhanced the GABA_\text{A}-mediated tonic conductance in rat hippocampal CA1 neurons by turning on high-affinity GABA_\text{A} receptors. In mouse dentate gyrus granule cells, acute application of insulin increased GABA_\text{A}A-mediated phasic conductance. The results demonstrate that insulin differentially regulates the inhibitory GABAergic transmission in the rodent hippocampus depending on neuronal types and sub-domains. This observation may provide a putative cellular mechanism underlying selective insulin action in multiple brain regions.
Tyrosine hydroxylase (TH), the rate-limiting enzyme in the synthesis of dopamine, is highly regulated notably by phosphorylation in several Ser/Thr residues of the N-terminal tail. However, the physiological role of phosphorylation at Ser31 site (THpSer31) still remains unclear. Here we report that TH microsomal fraction content decreases after inhibition of the kinases responsible for phosphorylation at Ser31 (Cdk5 and ERK1/2). Cellular distribution of overexpressed phospho-null mutant TH1-S31A was restricted to the soma of neuroblastoma, with decreased association to the microsomal fraction, whereas phospho-mimic TH1-S31E was distributed throughout soma and neurites. Microtubule disruption or co-transfection with α-synuclein A53T caused TH1-S31E accumulation in the cell soma. Moreover, in a mouse model of TH deficiency with decreased TH and catecholamines caused by the mutation Th-p.R203H, TH pSer31 immunoreactivity was present at low levels in the substantia nigra, and a dramatic reduction was seen in the striatum. Taken together, our data indicate that Ser31 phosphorylation may regulate the subcellular localization of TH through its transport along microtubule, notably towards the projection terminals. Our results open a new understanding of TH regulation by phosphorylation and reveal its interaction with key players in Parkinson’s disease, providing new research lines to understand dopamine synthesis in physiological and pathological states.
Spinal cord injury (SCI) results in sustained involuntary muscle contractions that may generate abnormal and chronic posture, dystonia, or sudden and temporally-defined muscle contraction, known as muscle spasms. The neuronal mechanisms for these aberrant motor responses are not well understood.

Here we used a mouse model of chronic SCI with a sacral lesion that exhibits an abnormal posture of the tail, characterized by sustained activity in small sized motor units (MUs), and spontaneous muscle spasms, characterized by a sudden activation of large sized MUs. After SCI optogenetic activation of excitatory spinal interneurons triggered and maintained spasms with temporally-defined recruitment of large MUs. Further in vitro calcium imaging in lesioned mice revealed a persistent neural activity in excitatory spinal interneurons during spasms. On the contrary, stimulation of excitatory neurons did not evoke a dystonic tail posture and the concurrent change in activity of the small MUs, indicating different circuits generating the two responses. However complete silencing of the calcium channels Cav 1.3 in all spinal neurons reduced both spasms and dystonia. When the Cav 1.3 channels were silenced in excitatory spinal neurons the mice developed dystonia, similar to the wild-type, but a decrease in spasms.

In conclusion dystonia and spasms may emerge from activity in different pre-motor neuronal circuits, whose motor output is generated by small and large MUs, respectively. However since the two motor dysfunctions are characterized by sustained activity of the MUs, the Cav 1.3 channels represent a shared neural mechanism, allowing output amplification.
Previous studies have shown an involvement of cholesterol in neurodegenerative diseases such as Huntington’s diseases (HD). However, the mechanisms underlying lipid disturbances in HD and whether they are secondary or primary in the pathogenesis of the diseases is not known. Using striatal neurons expressing mutant 120polyQ Huntingtin (Htt) expressing protein, we observed that the levels of lipoprotein receptors (LDLRs) are markedly reduced compared with controls. As cholesterol uptake occurs via the lipoprotein receptors that can be influenced by various factors, we are currently studied the mechanism in more detail. We focus on the E3ligase Myl1p/Idol and the PCSK9 that regulate the LDLRs via protein ubiquitination and lysosomal degradation, respectively. We have recently also shown that the cholesterol biosynthetic pathway involving SREBP signaling can be influenced by cytokines and by activation of the low affinity p75 neurotrophin receptor (p75NTR) by pro-NGF. This may suggest that neuroinflammation can influence lipoprotein receptors in vulnerable neurons in HD. The role of pro-NGF and other inflammatory factors in controlling lipoprotein metabolism in mutant Htt expressing neurons and in HD are currently under investigation.
Synaptic degeneration occurs early in Alzheimer disease (AD) pathogenesis and strongly correlates with cognitive decline. We thus aim to perform an unbiased proteomic study of a synapse rich region of the hippocampus, i.e., the outer molecular layer (OML) of dentate gyrus, in order to identify proteins underlying synaptic dysfunction in AD. This region is selected due to its important role in memory and cognition, and early involvement in disease progression.

We are using laser capture microdissection (LCM) to dissect the OML from subjects with mild AD and neurologically healthy controls (n=5 per group). Quantitative tandem mass tag mass spectrometry is performed on the microdissected OML and proteins with altered expression levels are subjected to pathway analysis. Prior to the studies on post-mortem human brains, we first examined how many proteins that could be identified in the rat OML. 45 µg of proteins microdissected from rat OML resulted in an identification of approximately 2313 protein hits by label-free mass spectrometry. The mass spectrometry data showed that proteins playing a role in synaptic signaling are highly abundant in the OML, which was a valuable verification of using this region.

The optimization in rat brain showed that the combination of LCM with mass spectrometry is readily implementable and we predict a high number of proteins to be identified also in human brain samples. To our knowledge, this is the first study aiming to pinpoint proteins underlying synaptic dysfunction in AD by specifically focusing on a vulnerable region of the hippocampus with synapse rich content.
Ischemic stroke is responsible for 10% of annual mortality rates worldwide, which is only expected to increase by 2030. Existing treatments (e.g. thrombolytic treatment) may dramatically improve functional outcomes, but their efficacy is largely contingent on the time elapsed between the stroke incident and the medical intervention, given that 2 million neurons are being lost every minute after the onset of stroke. Cell replacement therapy at the sub-acute or chronic stage offers the option of extending this narrow therapeutic window while addressing a key constituent of stroke pathophysiology, namely cell loss. In this study, we investigated potential synergistic effects of minocycline treatment and human neural stem cell (hNSC) transplants in an adult rat model of transient focal cerebral ischemia. Rats treated with a daily dose (3mg/Kg) of minocycline intraperitoneally for 14 days post-lesion (dpl) had less severe neurological outcome, measured using the Bederson scale, and a tendency towards smaller lesion volumes. Lesion volumes were measured based on the hyperintense areas on T2-weighted MR images. Immunohistochemical (IHC) analysis suggests enhanced hNSC survival as well as integration with host tissue and enhanced vascular remodeling around the graft area in the minocycline-treated vs. the non-treated group at 3 weeks post-transplantation. Finally, there was a significant downregulation in the expression of the pro-inflammatory cytokine TNF-α and the transcription factor HIF-1α in the minocycline treated group. This study suggests a positive effect of minocycline on neurological outcome after stroke and modulation of inflammation in order to enhance survival of transplanted hNSCs.
Motor neurons are highly polarized cells. Their somas and associated dendrites are located in the brainstem and spinal cord, while their axons traverse large distances in the body and connect to muscle via specialized synapses termed neuromuscular junctions (NMJs). Motor axons and NMJs are primary targets in amyotrophic lateral sclerosis (ALS). Muscle denervation and axonal retraction commence before motor neuron somas in the spinal cord are lost. The presence of ribosomes in axons indicates local protein translation, however the axonal RNA composition is largely unknown. We aimed to screen the RNA content of motor axons and somas in health and ALS by differentiating mouse embryonic stem cells (mESCs) into spinal motor neurons. We used mESCs overexpressing the mutant human superoxide dismutase 1 (SOD1<sup>G93A</sup>) gene to model ALS. The motor neurons were cultured in microfluidic devices, which allowed spatial separation of the motor neuron axons and somas. Deep RNA sequencing was performed on both the axonal and somatodendritic compartments to investigate local RNA composition. We identified the axonal transcriptome, with >5000 transcripts detected in motor neuron axons, of which around 10% were enriched in the axonal compared to the somatodendritic compartment. Moreover, we observed alterations in the localization of several transcripts in SOD1<sup>G93A</sup> motor axons versus wild-type controls.
Synaptic degeneration and accumulation of aggregated amyloid β-peptides (Aβ) are hallmarks of the Alzheimer diseased brain. Aβ is produced by sequential cleavage of the amyloid precursor protein (APP) by the β-secretase BACE1 and by γ-secretase. If APP is cleaved by the α-secretase ADAM10 instead of BACE1, no Aβ will be generated. BACE1 is active in the acidic environments of endosomes and Golgi whereas ADAM10 has been reported to mainly localize to the plasma membrane, especially to the postsynaptic density. Previously we have shown that both ADAM10 and BACE1 are highly enriched in synaptic vesicles of rat brain and mouse primary hippocampal neurons. Here we investigated the in situ synaptic localization of ADAM10 and BACE1 in adult rat and human brain. We used brightfield proximity ligation assay (PLA) to visualize the proximity of ADAM10 and BACE1 with the presynaptic marker synaptophysin and the postsynaptic marker PSD-95. PLA of ADAM10 and BACE1 with their substrate APP was also performed. We show that ADAM10 and BACE1 are present at both the pre- and the postsynaptic side in adult rat brain hippocampus as well as in human brain. Furthermore, the pre- and postsynaptic distribution of ADAM10 and BACE1 seem to be similar. Both enzymes co-localize with APP to a large extent. Preliminary results indicate that, compared to control, less ADAM10 but more BACE1 co-localizes with APP in the cortex of AD brain.
This is the first study to investigate passive perception of musical rhythms in Parkinson's disease (PD) using fMRI. Our aim was to investigate disrupted brain function in PD in using musical rhythms, to gain knowledge into why and how rhythm based music therapies are effective in the disease. Patients and healthy controls listened in this oddball paradigm to two rhythms of different complexity with intermittent beat omissions while being examined with fMRI.

We found significant group differences across complexity and time. While PDs generally show widespread higher brain activation listening to musical rhythms, it follows a specific pattern where listening to simple rhythms over the course of a few seconds, aligns the PD-brain with the healthy controls (HC) and the difference in activation patterns between the groups are significantly decreased. This normalization of brain activity does not occur with the more complex rhythm, where there is a more time-consistent higher level of activation in PD compared to HC. More importantly, the putamen shows higher bilateral activity for simple than complex rhythm, which might trigger the normalization of brain response to simple but not complex beat-based rhythm, since musical rhythms is known to drive basal ganglia activity. Inversely, listening at a complex rhythm caused frontal activity in detecting more complex omissions. Areas such as the planum temporale, basal ganglia, hippocampus, middle cingulate cortex, insula show interesting patterns of activation across contextual complexity and groups. Time-dependent activity differences between patients with Parkinson’s disease and the healthy control group interacts with rhythmic complexity.
Protein kinase C (PKC) is a family of kinases with 10 isoforms identified in humans. Because of their importance in memory formation they are sometimes called memory kinases. Aberrant PKC activity or reduced PKC levels have been reported in Alzheimer's disease (AD) patients. In addition there are studies showing that PKC activator bryostatin-1 has positive effects on memory, amyloid beta pathology, neuronal viability and lifespan in mouse models of AD. We have previously described and characterized small molecule PKC modulators, isophthalate derivatives, which activate PKC via the same mechanisms as bryostatin-1, by binding to the diacylglycerol-responsive C1 domain. In this study, we have characterized the effects of selected isophthalate derivatives in several cell-based models of AD. In a mixed culture of mouse primary neurons and BV2 microglial cells (an in vitro model of neuroinflammation) the isophthalates show neuroprotective effects and reduce the markers of inflammation induced by lipopolysaccharide (LPS). In human amyloid precursor protein (APP751) overexpressing SH-SY5Y cells the compounds increased secretion of the neuroprotective soluble APP and decreased production of the neurotoxic β-amyloid (Aβ). Our data from various cell-based models support the idea that PKC activation is beneficial for treating several aspects of AD and that small-molecule PKC activators could provide an attractive option for treating AD.
It is well established that amyloid plaque forming mice with transgenic mutated human APP show neuronal hyperactivity and epilepsy in their young adulthood; however, no data exist yet whether the hyperactivity persists until old ages. Our earlier microdialysis study revealed declined stimulated glutamate release upon aging in both wild-type and transgenic mice, which may reduce neuronal hyperactivity.

Setting out from this hypothesis, we implanted 16 APPswe/PS1dE9 male mice and 16 wild-type littermates at the age of 14-16 months with cortical screw electrodes, small electrodes bundles into medial frontal cortex (FC), thalamus, hippocampus (HC), visual cortex, and an EMG electrode on the neck muscles. Video-EEG was recorded for 2 h during 1-4 days when the single mouse was freely moving in a walled arena (diameter = 38 cm). Power spectral density (PSD) of EEG was calculated for three behavioral states: movement, waking immobility and non-REM sleep (too little REM was recorded to allow analysis), and was further divided into delta, alpha, low-gamma and high-gamma frequency bands.

The PSD analysis revealed increased power in the neocortex in the aged mice similarly to young adult mice. In addition, a PSD increase emerged in HC with age, while the increased PSD in thalamus attenuated. Analysis is ongoing on phase-amplitude coupling between frontal delta and gamma oscillations, and between hippocampal theta and gamma oscillations. The hyperactivity/hypersynchrony in HC that emerges with aging may be associated with spatial memory impairment that manifest around 12 months of age in this AD mouse model.
Aim: Utilizing microelectrode arrays (MEAs) we aim to study network dynamics of *in vitro* engineered motoneuron cultures and their response to opto- and chemogenetic modulation to model pathophysiological aspects of spinal cord injury. Electrical stimulation through the MEA is used to induce stimulus-response patterns, which provide a network-specific measure to modification. With a computational model of the network, predictions of firing pattern learning rate is achieved.

Method: Motoneurons derived from induced pluripotent stem cells (iPSCs) are cultured on MEAs (Multichannel Systems) for 3 months. Utilizing DREADDS, specifically against inhibitory hM4Di and excitatory hM34Dq, as well as NMDA and AMPA receptors, the network activity can be modulated on demand by administration of clozapine-N-oxide to influence the learning of the firing pattern. Simultaneously, this modulation provides a measure of fit for the computational model of the network prior to injury modelling. For computational modelling, a random Boolean network model is established for each culture.

Results: Cultures have been established and maintained on MEAs for 6 months, with robust stimulus-response patterns present from 40 to 200 DIV. Post-hoc computational modelling of network dynamics has been established.

Conclusion: Motoneuron culture on MEAs provides a suitable *in vitro* model for spinal cord injury. When coupled with task learning and computational models of network activity, detailed analysis of network response to injury is possible. Future outlooks include creating structured motoneuron networks and myotube co-cultures on microfluidic systems, and 3D culture on MEAs.
Metabolic support of neurons by glial cells is impaired in ALS, which considerably contribute to the pathophysiological progress of the axonal damage during the course of the disease. We developed an electrophysiological set-up for in vivo recording of CNS fibers in the fasciculus gracilis of the spinal dorsal column. We measured nerve conduction velocity (NCV) as well as determined fatigue of stimulated axons by analyzing the compound action potential (CAP) during tetanic stimulation of different frequencies. In a previous study, we could detect significantly faster drop of the CAP amplitude upon high-frequency tetanic stimulation in mice lacking the NMDA receptors in oligodendrocytes when compared to wild-type litters. In this study, we measured a decrease of NCV and a higher fatigue of spinal axons in wild-type mice during metabolic challenge induced by an increase of the anesthetic state. This NCV and fatigue changes were ameliorated by the supply of the metabolic substrate lactate which was shown to be secreted by glial cells and metabolized by axons for ATP generation. In the SOD1G93A mouse model of ALS, during clinical stages NCV and fatigue were impaired comparing the values of wild-type litters. In the ALS mice, an amelioration of the NCV and the fatigue of spinal axons was also observed with lactate supply.
Alzheimer disease (AD) and Dementia with Lewy bodies (DLB) are two most common forms of dementia disorders representing almost 70-80% of dementia population. The pathology of AD is very complex and is not understood completely yet. However, presence of extracellular senile plaques made up of amyloid-β peptide and neurofibrillary tangles (NFTs) made up of microtubule associated protein tau in the diseased brain are two major hallmark of AD. Lately, the research efforts have been made towards management of tauopathy because of repeated failures of anti-amyloid antibodies. It has been reported [1, 2] that heat shock protein-90 (Hsp90) plays an important role in the prevention of protein misfolding and aggregation with the help of several co-chaperones. Especially, cis-trans peptidyl-prolyl isomerase FK506 binding protein 51 (FKBP51), coordinates with Hsp90 to provoke tau pathogenesis by reducing tau β-sheet amyloidosis [3]. In order to elucidate the role of FKBP51 in tau metabolism, here, we report the crystal structure of FKBP51 at a resolution of 2.4 Å. It consists of an N-terminal PPI domain and a C-terminal TPR domain, which binds to C-terminal of Hsp90 and mediates the chaperoning action. Our study would help in understanding the molecular mechanism of the FKBP51 co-chaperone involved in tau degradation and would also help in the design and development of small molecules aimed to inhibit such chaperoning mechanism.


The basal ganglia (BG) play a crucial role in a variety of motor and cognitive functions. The two input nodes of the BG (striatum and sub-thalamic nucleus -STN) and the intermediate node (globus pallidus external -GPe) converge at the globus palidus internal (GPi). Thus, the control of cognitive and motor behaviour depends on how task-related responses in the striatum and GPe and STN affect the inhibitory output of the GPi. Whether striatal, GPe and STN input can alter the activity in GPi depends not only on the strength of the input but also on the state of ongoing activity of the GPi.

Here we analysed the statistics of the ongoing spiking activity recorded from GPe, GPi and STN of healthy and MPTP treated monkeys. We found that as compared to healthy state, in Parkinson disease (PD), STN and GPi spike at higher rate, whereas the mean firing rare of GPe neuron was decreased. Interestingly, in PD, GPi neurons showed higher variability in their firing rate even though the temporal variability in STN and GPe remained unchanged. We used a computational model of the BG to understand the functional consequences of increased variability of GPi. We found that variability in the GPi firing rate decreases the signal-to-noise ratio and therefore, only very strong task-related activity from the striatum, STN and GPe is able to alter GPi firing rates. These results suggest that temporal variability in GPi plays an important role in the manifestation of PD symptoms.
Training of the next generation of neuroscientists in Norway facilitated by the Norwegian Research School in Neuroscience (NRSN) and the Norwegian Neuroscience Society (NNS)

Presenter: Tanja Isabelle Doller - Norwegian Neuroscience Society
Theme: Neurodegenerative Disorders and Injury
Posterboard number: 4
Time of presentation: Friday June 9 - 1200-1400

Neuroscience in Norway aims for cutting edge science by combining disciplines, bridging clinical research and molecular/cellular biology, as well as computational modelling, to better understand human health and disease. Key to achieve this is high quality training and representation of all related disciplines and practices in Norway. Neuroscience research and education is the responsibility of several public players, and is facilitated by the Norwegian Research School in Neuroscience (NRSN) and the Norwegian Neuroscience Society (NNS).

NRSN coordinates and improves educational activities for PhD candidates in neuroscience. By combining the specific expertise of four partner institutions (Norwegian University of Science and Technology, University of Oslo, University of Bergen and Norwegian University of Life Sciences), and the affiliated Arctic University of Norway, NRSN aims to facilitate PhD research training that will enable the next generation of neuroscientists to face the great challenges and opportunities in the field.

The aim of NNS is to stimulate advances in Norwegian neuroscience, through representation of all neuroscience related disciplines and practices, facilitation of neuroscience research and education, and to disseminate information about neuroscience research and applications to the general public. NNS represents the interests of neuroscientists in Norway vis-à-vis appropriate Norwegian institutions, including legislators, policymakers, the press, and funding agencies engaged in supporting and promoting neuroscience research and education.

Norwegian Neuroscience is embedded in a professional international network. PhDs at NRSN profit from the accreditation as European Neuroscience School (NENS) and NNS formally represents neuroscience in Norway at the Federation of European Neuroscience Societies (FENS).
Birth asphyxia is one of the leading causes of neonatal mortality globally, and it imposes an enormous individual and societal disease burden. Seizures are common after birth asphyxia, and they are generally thought to contribute to the hypoxic-ischemic encephalopathy (HIE). Our aim was to establish a rodent model of term intrapartum asphyxia to study pathological mechanisms of HIE.

Pronounced functional changes take place in the human brain during the perinatal period, as evidenced by the emergence of continuous cortical EEG. In rats, similar changes occur around postnatal day 11, which was chosen as the term equivalent age for the model. P11 is also the age when the expression of the neuron-specific carbonic anhydrase CA7 isoform commences, providing a molecular marker for cross-calibration of the human and rodent stage of cortical development.

Freely moving rat pups implanted with epidural cortical electrodes were exposed to 30 min of experimental asphyxia (9/5% O₂ plus 20% CO₂ gas mixture). Seizures with rearing and tonus-clonus appeared within the first minutes of recovery in air, and they were paralleled by a crescendo of spike and wave discharges in the EEG. Contrary to this, no seizures were observed when the first 30 min of recovery occurred in 5% CO₂ gas (graded restoration of normocapnia, GRN).

The time course of post-asphyxia seizures and blood-gas analyses indicate that our P11 rat model closely mimics the key aspects of human birth asphyxia, thus enabling detailed studies on the pathophysiological mechanisms, as well as designing novel therapies, such as GRN.
Amyotrophic Lateral Sclerosis (ALS) is a relatively common progressive neurodegenerative disease that primarily affects both upper and lower motor neurons. A wide range of mutations has been identified as causing the disease, but while our knowledge concerning underlying mutations has been rapidly expanding in recent years, our understanding of the molecular pathology – particularly the onset and mechanism by which the respective mutations cause the disease – remains lacklustre. To enable the investigation of some aspects of these mechanisms we are establishing a testing platform using motor neurons obtained by direct conversion and reprogramming via induced pluripotent stem cells of patient-specific cells. The platform’s potential to study behaviour of these cells in vitro will be supplemented by employing Multielectrode arrays (MEAs). The use of MEAs will allow us to examine the electrophysiological behaviour of small networks of these cells as well as observing dynamic changes in the network after insult. The combination of these cellular and electrophysiological platforms will enable acquisition of new insights into both pathological mechanisms (including age-related factors) of specific mutations as well as network behaviour and plasticity under a range of external stressors suspected to be environmental risk factors for ALS.

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Stroke is the third leading cause of mortality and disability-adjusted life-years (DALYs)[1],[2] worldwide. Ischemic stroke may be caused by an embolus or thrombus, which restricts blood flow to the affected region of the brain, setting off a molecular cascade ultimately leading to cell death.[3] The insult occurs within an irreparably damaged core ischemic area surrounding the blood supply and within a more peripheral ischemic penumbra, which is potentially salvageable[4] for up to 4.5 hours after stroke onset.[5] However, only 5-15% of patients qualify to receive acute treatment.[6] To address this problem, in vitro assays are emerging as important models to supplement existing in vivo strategies. In the following, the viability and neuroprotection of the pre- and posttreatment rescues: DHA and minocycline were compared to no treatment across rat cortical cells, human neural stem cells (H9 cells), rat neural stem cells and rat astrocytes in 2D monocultures undergoing oxygen glucose deprivation (OGD) or kainate treatment. Preliminary results indicate that individual cell types prefer the minocycline treatment and the pretreatment rescue to varying degrees and respond differently to the ischemic insult, demonstrating the complexity of the ischemic microenvironment. In the future, cortical cell-astrocyte co-cultures will undergo the same rescue treatments in combination with OGD in microfluidic 3D chips with predefined microtopographies. Cell viability and inflammation will be compared to monocultures of the same cell types undergoing the same procedure in 2D static wells to obtain more comprehensive and realistic results.

Cholesterol is one of the most important molecules of eukaryote cells and is involved in many neural processes. An imbalance of cholesterol homeostasis has been correlated with neurodegenerative and neurodevelopmental disorders such as Autism Spectrum Disorders (ASDs). Autism spectrum disorders (ASDs) are a group of developmental disabilities characterized by social-communication deficits, restricted and repetitive behaviors and by a delay of cognitive functions. Interestingly, both the incidence of ASD and cholesterol homeostasis display sex-related differences. Despite these observations, no systematic studies on the protein network of cholesterol homeostasis maintenance in ASDs have been performed. Here we analyzed, in six different brain areas (amygdala, cortex, nucleus accumbens, cerebellum, hippocampus and striatum), the protein network of cholesterol metabolism in adult rats prenatally exposed to valproic acid (VPA), a well-established experimental model of autism. Our attention has been focused on alterations in both the key enzyme of cholesterol biosynthetic pathway (3-hydroxy 3-methylglutaryl Coenzyme A reductase) and the receptors involved in the uptake of lipid (Low Density Lipoprotein receptor, Low density lipoprotein receptor-related protein 1, and Scavenger receptor class B member 1) in male and female adult rats. The results show that rats exhibit sex-dependent differences of both the autistic phenotype and the proteins involved in cholesterol homeostasis suggesting for the first time a possible correlation among cholesterol homeostasis maintenance, ASDs and sex.
**Introduction:** Parkinson’s disease (PD) is characterized by the formation of intracellular Lewy bodies ($\alpha$-synuclein containing aggregates) in the brain and loss of dopaminergic neurons in the substantia nigra pars compacta, with subsequent degeneration of the nigrostriatal pathway. The exact mechanisms of the disease are still poorly understood and there is no curative treatment available, highlighting the need for more research.

**Method:** As an in vitro basis for studying PD, patient specific and control human fibroblasts are converted into dopaminergic neurons through viral and chemical patterning factors mimicking the chemotemporal situation of the developing ventral midbrain. Network plasticity and response to insult can be manipulated and monitored using tailored microfluidic chips and multielectrode arrays (MEAs). Designer receptors exclusively activated by designer drugs (DREADDs) selectively activate or inhibit the activity of the dopaminergic neurons through addition of clozapine-N-oxide (CNO) to the culture, thus providing a means of selectively altering network activity and influencing its dynamics and connectivity. In addition, CRISPR can be used to correct patient specific genetic mutations, while preformed $\alpha$-synuclein fibrils can be used to recapitulate the propagation of $\alpha$-synucleinopathy seen in PD patients.

**Results:** We have converted human fibroblasts into induced pluripotent stem cells (iPSCs), as well as iPSCs into TH$^+$ dopaminergic neurons, which exhibit appropriate morphology, respond to dopaminergic stimulation, and form functional networks on MEAs.

**Discussion:** We are adapting our protocols to accommodate patient specific cell conversion, as well as molecular manipulations incorporating DREADDs, CRISPR and $\alpha$-synucleinopathy to further aid the understanding of disease mechanisms.
D10: Amyloid beta oligomers induce drebrin disappearance from dendritic spines via histone deacetylase activity
- Y. Ishizuka, T. Shirao

Presenter: Yuta Ishizuka - University of Bergen
Theme: Neurodegenerative Disorders and Injury
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Synaptopathy is observed in various cognitive disorders, including Alzheimer's disease (AD). Amyloid beta toxicity is mediated not only by the fibrillar form of the protein, but also by the soluble oligomers (Amyloid beta-derived diffusible ligands, ADDLs). Drebrin is an actin-binding protein that is located at mature dendritic spines. It is thought that drebrin is closely associated with cognitive functions because drebrin expression is decreased in AD brains and in cultured neurons exposed to ADDLs. Recent studies show that histone deacetylase (HDAC) activity is elevated in the AD mouse model, and that memory impairments in these animals can be ameliorated by some HDAC inhibitors. In this study, we examined whether inhibition of HDAC activity protect the ADDL-induced decrease in drebrin at dendritic spines. We show that ADDLs reduce the cluster density of drebrin along dendrites without reducing both drebrin expression and dendritic spine density. Suberoylanilide hydroxamic acid (SAHA), an inhibitor of HDAC significantly attenuated the toxic effect of ADDLs. In comparison, SAHA treatment did not affect the density of drebrin clusters or dendritic protrusions. Therefore, SAHA likely inhibits ADDL-induced drebrin disappearance from dendritic spines by stabilizing drebrin in these structures, rather than by increasing drebrin clusters or dendritic protrusions. Taken together, our findings suggest that HDAC is involved in ADDL-induced synaptopathy, and that the regulation of histone acetylation plays an important role in modulating actin cytoskeletal dynamics in dendritic spines under cellular stress conditions, such as ADDL exposure. Furthermore, this study raised the possibility of novel therapeutic approach using HDAC inhibitor for synaptopathy.
The optic tectum is central for multisensory integration and motor control of orientation. Over the past years, we have explored tectal function by using a conserved vertebrate system, the lamprey, as a reductionist model that offers the necessary accessibility through several novel preparations (Kardamakis et al 2015, 2016).

We found that visual and electrosensory sensory inputs converge onto the same projection neurons, which control gaze movements via monosynaptic excitatory connections. Evoked synaptic currents from the two inputs summate, thus, potentiating each other when they are aligned in space and time. With these conditions, the tectal inhibitory system allows response enhancement, which aims at increasing their spiking probability with spatiotemporal correspondence. However, when inputs arise from surrounding areas or are temporally misaligned, they instead suppress each other. These spatiotemporal computations are elaborated by local GABAergic interneurons in the superficial/intermediate layers within tectum. Furthermore, a subset of these interneurons establishes long-range horizontal connections that trigger global inhibition and give rise to rivalry across the tectal map of space, thus, controlling stimulus selection.

Our findings reveal that the optic tectum is not merely a passive recipient of pre-programmed gaze commands elaborated by upstream circuits but rather can perform complex sensorimotor processing, thus, implementing the final programs for motor behavior in its own right. Following the phylogenetic model, the circuit configuration giving rise to these rules we postulate be similar in later vertebrates. We are now testing the validity of these predictions in the superior colliculus by using mice as a generic mammalian model.
Our ability to encode acoustic signals to the brain depends on this highly specified and functional cochlear nervous system. Two types of neurons coexist in the cochlea. The type I neurons constitute the majority of the neurons and are the principal carrier of the auditory signal. On the other hand, despite many speculations, the contribution of the type II population to hearing is still unknown. Moreover, the type I auditory afferents have long been seen as a homogeneous population of neurons, acting as a simple relay between sensory receptors in the periphery and neurons of the central nervous system. However, like other sensory modalities, the auditory sensation is a composite of multiple features. These participate in our perception of sound frequency but also intensity, timbre and pitch, and in the selection of important speech in a background noise. This raises the question as to whether different subtypes of SGNs, beyond the classic type I and II subdivision, could participate in a peripheral encoding of these diverse features, as seen with the neuronal diversity in the somatosensory or visual systems. Here, we use genetically labelled, single cells for identifying the genetic profile by mRNA sequencing (RNAseq) of adult cochlear neurons. We identified 4 neuronal clusters in adult. One small cluster (Cl.i, 4.5%) expresses peripherin, but also tyrosine hydroxylase (TH) and plk5. The three other clusters are equally represented amongst the rest of the neurons and differentially express the transcription factors runx1 and Pou4f1 and the calcium binding protein calbindin and calretinin.
In vertebrates, olfactory information from one nostril is sent to the ipsilateral olfactory bulb (OB) and then to the olfactory cortices. Interestingly, the fish OB receives projections from contralateral olfactory structures. This includes projections from the contralateral fish homolog of the olfactory cortex and from the contralateral OB. However, this interhemispheric olfactory circuit remains poorly characterized. The goal of this study is to examine the extent of this interhemispheric circuit as well as its functional consequence on odor processing in adult zebrafish. Using ex vivo brain explants and fluorescent dye electroporation, we first confirm that the OB receives projections from the contralateral olfactory cortex and bulb. We further show that projections from the olfactory cortex are diffuse and mostly terminate at the inhibitory OB granule cells layer. On the contrary, projections from the contralateral OB are topographically organized and terminate at the superficial layers. Using 2-photon imaging in brain explants expressing the calcium indicator Gcamp6 in mitral cells, we show that information coming from one OB can significantly alter odor responses in the contralateral OB, eliciting a balance of excitation and inhibition. Finally, preliminary data indicate that interhemispheric OB connections help preserving mitral cell responses to a reproductive pheromone, when it is presented together with increasing concentrations of background odor. Altogether, our results provide a previously undescribed function for the interhemispheric neural circuit connecting olfactory structures. We propose that this circuit facilitates the detection of odors important for survival in the noisy olfactory environment encountered in the wild.
Sensory feedback from skeletal muscles is essential for coordinated motor control. The gatekeepers of this feedback are the proprioceptive sensory neurons (PSNs) sitting in the dorsal root ganglia. PSNs include subtypes Ia, Ib, and II, differing in anatomy and physiology. Currently, only electrophysiology could discriminate the PSNs subtypes, critically hindering investigations into these important neurons and the sensory-motor circuits of which they are a part. Here we address this problem, uncovering the genetic identities of the PSN subtypes in mice using a combination of mouse genetics, retrograde tracing and single cell transcriptomics.

We have achieved single cell transcriptome profile of PSNs at both embryonic stage E16.5 and adulthood. 297 E16.5 PSNs are clustered into subclasses, of which genetic markers are examined by RNA-ISH. We have successfully employed retrograde tracing of Ia PSNs by injection of Rhodamine-Dextran in the ventral spinal cord of E16.5 embryos. The identities of the subclasses by co-localization of their genetic markers and Rhodamine positivity, suggesting one subclass to be most probably Ia PSNs.

Similarly, 1302 adult PSNs are clustered into subclasses unbiasedly. Using Egr3::WGA mice in which Ia and II PSNs are filled with wheat germ agglutinin (WGA), we are currently validating the identities of adult PSNs subclasses by co-localization analysis of their genetic markers and WGA. To match with subtype-specific anatomy, we will further investigate those subclasses by looking into their synaptic partners using immunohistochemistry.

Our final aim is to generate mouse lines to allow in vivo and in vitro labelling and manipulation of PSNs subtypes.
Visual perception is not confined to a stationary vantage point. Mammals are in constant motion and need to incorporate information about the moving world, with information about self-generated movement to effectively perceive and interact with the environment. Functional investigations into the visual cortex have largely been limited to anesthetized or head-fixed animals, making the impact of movement relatively uncharted. Studies with head-fixed animals show large effects of movement-speed on visual cortical modulation, but little is known about visual processing in freely moving animals. Using chronically implanted electrodes, we investigate the impact of movement on orientation tuning in units recorded in primary visual cortex (V1) of rats. We find a population of units in the deep layers of V1 that show remarkable robustness in their orientation tuning despite heavy movement by the rat. These movement resistant orientation stable (MROS) cells remain selective despite continuous tilt of the platform-floor producing angular displacement of the rat head. While simultaneously recorded units from neighbouring regions or other cortical layers in the V1 showed loss of orientation tuning, the MROS units remained highly selective. The MROS cells also appear to display an evoked latency delay compared with the control orientation selective cells. The deeper layer location of the cells is interesting due to their potential impact in the columnar circuitry. Recent findings show deeper visual cortical layers can modulate and down-regulate incoming visual input. These cells might play a role in this down-regulation by incorporating locomotor or vestibular information.
The development of disc hernia related low back pain is associated with intervertebral disc rupture and leakage of the disc's inner core, nucleus pulposus (NP). The ensuing inflammatory response has been suggested to contribute to the increased evoked activity in ascending pain pathways. However, the degree to which NP alters the excitability and spontaneous activity in sensory afferents is unknown.

Using an acute ex-vivo adult mouse model in which hindlimb nerves together with the spinal cord are isolated perfused using artificial cerebrospinal fluid, electrophysiological records were obtained from de-sheeted sensory afferents in the saphenus nerve following acute exposure to NP. The degree of spontaneous firing including the frequency and burst pattern are compared to naïve preparations.

The results indicate that sensory afferents rapidly increase their firing rate following direct exposure to nucleus pulposus. The increased activity appears within 15 seconds and lasts for up to 30 minutes with the mean firing frequency increasing to 217% (p<0.05) after 30 seconds and by up to 600% in individual nerves. In the presence of nucleus pulposus the firing pattern increasingly consists of intermittent bursts of high frequency neuronal activity.

The presence of nucleus pulposus potently increases the spontaneous firing rate of sensory afferents. The results thereby support an important role for NP in the generation of disc hernia related pain and could indicate possible pharmacological targets for more efficient treatment of low back pain.
The rodent Globus Pallidus (GP) has recently been shown to consist of at least two main neuronal populations that differ in their electrophysiological, morphological, and molecular properties. Here, we studied the synaptic inputs underlying spontaneous activity and sensory integration in the mouse GP. We obtained in-vivo whole-cell recordings in the GP of anesthetized mice and used light pulses delivered through the patch pipette to classify the recorded neurons based on their expression of ChR2. All GP neurons exhibited slow-wave modulated activity: prototypical cells exhibited a decrease in discharge rates during cortical ‘up’ states whereas arkypallidal cells were depolarized and fired action potentials. Hyperpolarization of prototypical cells by current injection revealed barrages of synaptic inputs during ‘up’ states, similarly to arkypallidal cells. Both cell types responded to whisker deflections by a multiphasic sequence of excitatory and inhibitory events. The input sequence began with an immediate excitatory component followed by a fast inhibitory synaptic input. Sensory responses were largest when bilateral whiskers were stimulated, while unilateral deflections evoked significantly weaker responses. These initial sensory responses were often followed by a slower inhibitory component. Multiphasic responses were evoked in both cell types, however, the tonic firing of prototypical cells resulted in sensory evoked pauses while in arkypallidal cells sensory responses were depolarizing and evoked action potential discharge. Our data suggests that the different GP cell types receive largely similar spontaneous and sensory-evoked synaptic inputs. However, the impact of these inputs on their respective activity patterns is largely shaped by intrinsic membrane properties.
Diabetic retinopathy (DR) affects RGCs and glial cells. Polysialylated neural cell adhesion molecule (PSA-NCAM) is abundantly expressed by astrocytes and Müller cells in the adult retina in close proximity to RGCs. It has been demonstrated that PSA-NCAM supports survival of RGCs following injury. The aim of our study was to investigate whether or not DR is associated with alterations in the PSA-NCAM levels and distribution in adult mice retina.

Swiss Webster male mice at 1.5 months of age were made diabetic by intraperitoneal administration of streptozotocin. Examination of the retinas of diabetic mice revealed considerable reduction in the density of RGCs after two months of diabetes development. Our experiments demonstrated reduction in the PSA-NCAM immunoreactivity in the inner part of the retina where RGCs are located. In contrast, an enhanced PSA-NCAM immunoreactivity was found in the middle and outer retinal parts, where PSA-NCAM was co-localized with GFAP in the Müller cell branches.

It is proposed that decreased levels of PSA-NCAM in the inner part of the retina might be responsible for the degeneration of RGCs. An increased expression of PSA-NCAM in the processes and soma of Müller cells possibly induce their hyper-reactivity and processes outgrowth.
Perineuronal nets (PNNs) are specialized extracellular matrix structures, which envelop the cell soma and proximal neurites of subpopulations of neurons, mostly parvalbumin positive inhibitory neurons. PNNs develop postnatally with complete assembly by the end of the critical period that is associated with peak levels of brain plasticity. Enzymatic degradation of PNNs using the bacterial enzyme chondroitinase ABC (chABC) has been shown to reopen juvenile levels of plasticity in the adult cortex, suggesting that PNNs contribute to stabilize synapses and limit the level of plasticity in the adult brain. However, as chABC is not specific to PNNs it remains unclear if the increased plasticity results from PNN removal or the other effects of the enzymatic activity.

To address this we tested a novel conditional knockout mouse where the gene for aggregan (ACAN), a key component of PNN, can be deleted in a Cre-dependent manner. Adeno-associated viral vectors with Cre recombinase was injected into the primary visual cortex (V1) of adult ACAN(tm/tm) mice.

Experience-dependent plasticity was induced by monocular deprivation (MD) for four days, which suffices to induce an ocular dominance (OD) shift in juvenile animals. The effects were assessed using optical imaging of intrinsic signals to assess ocular dominance plasticity in the binocular region of V1. We show that conditionally knocking out the ACAN gene leads to an elimination of PNNs and increase OD plasticity in the adult mouse visual cortex.
In all organisms, humans and insects included, the olfactory sensory neurons establish a direct contact between the external environment and the brain. In noctuid moths, a few female-produced molecules activate the male-specific olfactory system. Each of these (biologically relevant) odor stimuli is associated with an easily recognizable glomerulus in the macroglomerular complex (MGC) forming a part of the insect antennal lobe (corresponding to the mammalian olfactory bulb). This male-specific arrangement is linked to two well-defined behavioral responses, one ensuring attraction and mating behavior by carrying pheromone information released by conspecific females and the other inhibition of attraction via information emitted from heterospecifics. Previous data have demonstrated that MGC PNs project along all three classical antennal-lobe tracts (ALTs), the medial, mediolateral, and lateral ALT (corresponding to the olfactory tract in mammals). So far, however, individual MGC PNs of moths have been identified almost only in the medial ALT. These medial-tract PNs convey information to regions in the calyces and lateral horn distinct from those targeted by PNs tuned to general odorants. In this study, we performed intracellular recording and staining from individual MGC neurons in the moth *Helicoverpa armigera* for exploring the physiology and morphology of male-specific neurons confined not only to the medial ALT but also to the other tracts. We have identified several new types of MGC PNs, passing along the lateral as well as the mediolateral ALT. All the neurons responded to antennal stimulation with female-produced compounds, including the two behaviorally significant pheromone compounds and/or one interspecific signal.
Single-cell RNA sequencing is a powerful tool to identify biological cell types. Isolating single adult neurons is experimentally challenging and we have therefore established a protocol based on isolation of single neuronal nuclei. Here, we show the results of single-nuclei RNA sequencing (snRNA-seq) of cortical interneurons and we compare these results with a dataset obtained from single whole-cell RNA sequencing. We have further applied our snRNA-seq approach to define the identify of presynaptic populations after transsynaptic rabies tracing. We find that the snRNA-seq protocol allows us to identify neuron type clustering similar to that obtained with whole-cell sequencing, and is further compatible with connectivity mapping with rabies virus.
Finding accurate electrophysiological markers of consciousness is of clinical as well as theoretical importance. They may lead to tools that can help clinical staff to correctly classify states of consciousness in patients. Furthermore, such markers may inform the validity of theories of consciousness, to bring us closer to an understanding of the necessary and sufficient conditions for consciousness.

Here, we present preliminary findings from research carried out in collaboration between the Oslo University Hospital and the University of Oslo. Over the last years, our teams have performed sets of experiments, in which participants underwent different forms of anesthesia while brain activity was measured by EEG. From the EEG data, putative electrophysiological markers of consciousness were calculated, and compared with the participant's report of conscious state.

Based on preliminary analyses of our data, we show that the Directed Transfer Function (DTF) seems to hold promise as a potential electrophysiological marker of consciousness, as suggested in our earlier work (under review). Furthermore, we present preliminary results from direct comparisons between the DTF and other promising electrophysiological markers of consciousness, in their accuracy and efficiency in classifying the conscious state of individuals. Specifically, we calculate measures based on directed connectivity, coalition entropy, Lempel-Ziv complexity, and information integration (see e.g.: Schartner et al., 2015, PLoS ONE, 10(8)) on the same data sets, and discuss each of the measures’ merits as electrophysiological markers of consciousness, and their feasibility for functioning as real-time measures in clinical situations.

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Human nervous system lesions, such as spinal cord injury (SCI), often affect young persons, leading to extensive functional deficits. No clinical treatment offering functional improvement exists. Numerous promising preclinical studies including compounds, cell therapy and/or training have led to clinical trials. However, translation from animal models to the clinic has proven challenging. Species differences may be one explanation. To develop clinically potent and safe treatments and translate proof of concept findings in animal models to clinical settings, we also need models to study human species-specific injury and repair mechanisms.

To study human SCI we established an ex vivo human spinal cord slice culture model. We evaluated culture stability, their interaction with human allogeneic donor neural progenitor cells (NPCs) and a biometric scaffold. Human first trimester-derived spinal cord (cross sections, 250 µm) slices after informed consent by tissue donors and ethical approval from EPN, Medicine, Stockholm. Up to 21 days in vitro (DIV), immunohistochemistry, calcium imaging and electrophysiological analysis confirmed viability and spinal cord organotypic features of the slices. At 14 and 21 DIV, we observed an increased number of caspase-3+ cells and activated microglia in response to contusion injury in the slices compared to controls. However, a significantly reduced apoptosis and microglial activation was observed after neural cell therapy to injured slices. In addition, preliminary data suggest that human spinal cord-derived cells migrate and extend neurites along artificial biometric spider silk fibers.

We conclude, that human spinal cord slice culture is a promising model to study human injury and therapeutic strategies.
Stem cells are powerful tool to study human development, due to their capacity to differentiate to any specific cell type. However, strict legislations and ethical questions have restricted the research. Ten years ago the pioneering study of Yamanaka and colleagues discovered a novel method to produce pluripotent stem cells from adult somatic cells by introducing a set of defined reprogramming factors. This method circumvents the legislation problems of ES cells and brings human stem cells available for every lab bench.

The differentiation of human induced pluripotent stem (iPS) cells to functional neurons has been successfully carried out in several laboratories. However, the morphology of these neurons resemble to the morphology of immature neurons. The most striking differences in hiPSC-derived neurons compared to neurons in post mortem human brains are the atypically low density and abnormal structure of dendritic spines.

In this study we have used human iPS cells and optimized the differentiation protocols to achieve normal looking dendritic spines in high density. We have tested several growth factor and drug combinations and monitored the spine maturation in co-culture with other cell types. Although the project is still in progress, we have achieved promising improvements in culturing protocols. In order to compare the spine morphology of neurons differentiated from iPS cells derived either from healthy donors or humans with a variety of neurological diseases, it is fundamental that control neurons exhibit normal spines with normal density and in reproducible manner.
Anatomical location is a key parameter for interpretation and comparison of neuroscientific data. Location is typically determined by looking up diagrams in anatomical reference atlases, communicated using anatomical terms, and shown in representative images. But the documentation provided varies considerably among scientific publications. Often, essential information about nomenclature and reference atlases, or criteria used to define boundaries of structures, is missing. This lack of accuracy limits the opportunities for comparing and integrating data from different publications, and could lead to failure in replicating scientific experiments. To clarify and address this challenge, we have investigated current practice for assigning and documenting anatomical location for different categories of experimental neuroscience data reported in > 120 articles investigating the rodent brain. Our findings show that the specificity and accuracy of anatomical documentation in most cases can be considerably improved with relatively simple procedures. We here suggest some general and method-specific recommendations for such improvements, and discuss how these steps may contribute to increase the accuracy of anatomical descriptions and data interpretation. We demonstrate how new three-dimensional rodent brain reference atlases, and associated software tools for spatial registration of brain image data to a common anatomical space offer new opportunities for efficient integration and comparison of neuroscience data.
Abstract

Gelatin coating of brain implants is known to provide considerable benefits in terms of reduced inflammatory sequelae and long-term neuroprotective affects. However, the mechanisms for gelatin’s protective role in brain injury are still unknown. To address this question, cellular and molecular markers were studied with quantitative immunohistochemical microscopy at acute (<2 hours, 1, 3 days), intermediate (1-2 weeks) and long-term time points (6 weeks) after transient insertion of stainless steel needles into rat cortex cerebri with or without gelatin coating. Compared to non-coated controls, injuries caused by gelatin coated needles showed a significantly faster resolution of post-stab bleeding/leakage and differential effects on different groups of microglia cells. Moreover, the level of matrix metalloproteinase (MMP-2 and MMP-9, two gelatinases) was significantly altered with a strong initial release that rapidly fell significantly under control values. Neuronal populations and activated astrocytes were largely unaffected. In conclusion, the beneficial effects of gelatin may be the combined results of faster healing of the blood brain barrier curtailing leakage of blood borne molecules/cells into brain parenchyma and to a modulation of the microglial population response favoring restitution of the injured tissue. These findings present an important therapeutic potential for gelatin coatings in various disease, injury and surgical conditions.
Reference atlases of the brain are important tools for assigning location to data captured in neuroscience experiments. Spatial alignment of sectional images to reference atlases is, however, challenging to perform for several reasons. Manual approaches applied to large series of sectional images are time consuming and, moreover, histological sections are often cut at angles deviating from the principal anatomical planes presented in conventional reference atlases. Novel 3D reference atlases and accompanying tools provide new opportunities for rapid and accurate spatial registration and integration of data in common atlas space. We here present new tools for use with the Waxholm Space atlas for the rat brain and the Allen Mouse brain atlas, and workflow that allows users to 1) interactively generate customized atlas images (slices of the 3D reference atlas) corresponding to the plane of sectioning of any experimental image series, 2) superimpose atlas images onto experimental images using affine transformations to match key anatomical landmarks, 3) propagate the transformations across a series of images, 4) assign spatial reference atlas coordinates to the experimental images, and 5) allow viewing and analysis of the experimental data integrated in the reference atlas. We exemplify the workflow and use of our methods with a range of experimental data from neuroanatomical and neurophysiological investigations.

*Presenting author

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The RNAscope® assay provides a powerful method to detect gene expression within the spatial and morphological tissue context. The proprietary “double Z” probe design in combination with the advanced signal amplification enables a highly specific and sensitive detection of the target RNA with each dot visualizing a single RNA transcript. Therefore, this robust signal-to-noise technology allows for detection of gene transcripts at single molecule level with single-cell resolution analysis and can further expand our understanding of gene expression in cell lines and tissues samples. The multiplexing capabilities of both the chromogenic and fluorescent RNAscope® assays facilitate the simultaneous visualization of multiple targets in formalin-fixed paraffin-embedded (FFPE) and fresh frozen samples, enabling consistent characterization of cell populations within the nervous system. In summary, RNAscope® technology allows the visualization and quantification of virtually any gene from any genome in any tissue with unprecedented specificity and sensitivity.

Here we illustrate the utility of RNAscope® applications in neuroscience:

- Identification, characterization, and (co-) localization of both mRNAs and IncRNAs in the nervous system
- Identification, visualization and characterization of specific cell types in the nervous system
- Detection of mRNA in the nervous system when no (reliable) antibodies are available
- Visualization of neuronal network activity and plasticity
- Validation of target mRNA expression after high-throughput gene expression analysis
- Validation of (cell type-specific and conditional) genetic modifications
Recent years have seen the development of extraordinary molecular tools for neuroscience, from transgenes that allow the control or visualization of neuronal activity to precise and unambiguous neuroanatomical tracing systems. However, the full potential of such tools can only be realized if they are deployed with anatomical specificity that approaches the granularity at which neural circuits operate. This cell-type specificity can only be obtained by molecular genetic methods. To date this has involved using the specificity of native promoters to direct transgene expression, either by using minimal promoter constructs with viral vectors or pronuclear injections into oocytes, or by knocking the transgene directly into the native RNA transcript via homologous recombination. However, despite several initial successes, these techniques have serious limitations. Viruses and transgenic lines made with minimal promoters typically do not faithfully phenocopy native gene expression. Even knock-ins, which can do so, are limited by the fact that very few genes actually express exclusively in a single cell type. Therefore, all these approaches have fatal flaws. Leveraging precise tissue dissection techniques with ChIP-Seq of histone modifications associated with active enhancers, we have identified enhancers active specifically in particular brain regions. Combining these tissue specific enhancers with a mutated minimal promoter incapable of driving gene expression alone has allowed us to generate lines of transgenic mice, which target distinct cell types of particular brain regions. While our first proof-of-principle case targets distinct neurons of the Medial Entorhinal Cortex, this method can be used to target cells of any brain region. Ultimately, this enhancer-based approach should provide a means to deliver any transgene to any cell type in the brain, greatly enhancing our ability to understand the native circuitry of the brain at the level of granularity at which it operates.
In zebrafish and other vertebrates, the olfactory bulbs (OBs) play a crucial role in odor processing. Olfactory information from each nostril is relayed ipsilaterally to mitral cells (MC) in the OBs. The encoded stimuli can then be modulated and passed on from MCs to higher target areas, usually in the same hemisphere. Because inputs from the nostrils pass only through the ipsilateral bulbs, odor signals from each nostril are generally thought to be processed independently in each hemisphere. In contrast to this general assumption, our lab’s recent work suggests that MCs send direct projections to homologous regions of the contralateral bulb. Moreover, we have shown that these connections may be important for boosting the gain of odor-specific olfactory circuits, increasing signal quality in noisy environments.

In this study, we characterized further the functional connectivity of contralateral projections in the OBs. For this purpose, we developed an optogenetic stimulation system that uses a spatial light modulator (SLM) assembly. This system allows us to generate 3D holograms of blue light, which we can use to quickly and systematically scan different regions of the brain. By combining holographic stimulation of Channelrhodopsin-2-expressing OB neurons with intracellular recordings of individual MCs, we were able to build a detailed connectivity diagram of interhemispheric connections between OBs. Our results confirmed our initial finding that MCs in homologous regions of contralateral OBs exhibit direct and strong excitatory connections. Furthermore, these findings show that SLM-based optogenetic circuit mapping is an effective method for studying brain connectivity.