glial heterogeneity

SPP1757

Annual Meeting of
DFG Priority Programme 1757

Functional Specialisations of Neuroglia
as Critical Determinants of Brain Activity

Zons | Oct 26 - 28, 2017

HEINRICH HEINE
UNIVERSITÄT DÜSSELDORF

Meeting Site

Hotel Schloss Friedestrom

Parkstr. 2

41541 Dormagen-Zons

Scientific Programme

Thursday, Oct. 26, 2017

14:00 - 14:05	**Frank Kirchhoff/ Christine Rose**	**Opening remarks**
14:05 - 14:30	**Welcome notes**	
	Erik Lierenfeld	Mayor of the town of Dormagen
	Peter Westhoff	Vice President for Research and Technology Transfer, HHU
14:30 - 14:55	**Moritz Rossner**	*Glial-specific transcriptome analyses towards an SPP database*
15:00 - 15:25	**Daniela Dieterich**	*Astrocytic heterogeneity in morphology and protein synthesis – Is it tissue mechanics?*
15:30 – 15:55	**Ruth Beckervordersandforth**	*Adult gliogenesis and functional astrocyte heterogeneity in the hippocampus*
16:00 - 16:30	*Coffee Break*	
16:30 - 16:55	**Nicola Mattugini**	*Heterogeneity of astrocytes in white and grey matter in health and disease*
17:00 - 17:25	**Eva-Maria Krämer-Albers**	*In vivo analysis of exosome transfer using Cre-ERT2 mouse models*
17:30 - 18:30	**Nanna MacAulay**	*Glial management of activity-evoked K^+ transients - the Na^+/K^+-ATPase versus Kir4.1*
18:30	*Time for dinner and discussions in adjacent restaurants*	

Friday, Oct. 27, 2017

9:00 - 9:25	**Jovica Ninkovic**	*Glial heterogeneity in the adult zebrafish defines regenerative response*
9:30 – 9:55	**Dirk Dietrich/ Susanne Schoch-Mc Govern**	*Synaptic signal integration by NG2 cells*
10:00 – 10:25	**Christian Steinhäuser/ Gerald Seifert**	*Impact of AMPA receptors and Kir4.1 channels in grey matter NG2 glia on myelination, signal transmission and behaviour: Comparative studies in the hippocampus and cerebellum*
10:30 - 11:00	*Coffee Break*	
11:00 - 12:00	**Brian MacVicar**	*Neuro-glial interactions in the life and death of neurons*
12:00 – 13:30	*Lunch Break*	
13:30 - 15:30	**Poster Session**	
15:30 – 16:00	*Coffee Break*	
16:00 - 16:25	**Hauke Werner**	*Molecular heterogeneity of CNS myelin: Novel role and regional relevance of a chemokine-like signaling protein in brain function*
16:30 – 16:55	**Gesine Saher**	*In vivo responses in CNS glia to peripheral metabolic changes*

17:00 – 17:25	**Andrea Trevisiol**	*Visualizing glial support of axon function with metabolic sensors in transgenic mice*
17:30 – 17:55	**Johannes Hirrlinger**	*Metabolic heterogeneity of astrocytes in grey and white matter of the brain*
19:00	*Joint Dinner (Friedestrom)*	

Saturday, Oct. 28, 2017

9:00 - 9:25	**Christine Rose**	*Heterogeneity in astrocyte sodium signalling: Functional consequences*
9:30 - 10:30	**Christoph Fahlke**	*Glial chloride homeostasis*
10:30 - 11:00	*Coffee Break*	
11:00 - 11:25	**Andreas Faissner**	*Regulation of glial diversity and brain activity by the neural matrisome and the LRP1 receptor*
11:30 – 11:55	**Dieter Bruns/ Yvonne Schwarz**	*v-SNARE proteins in astrocytic functions and heterogeneity*
12:00 - 12:25	**Frank Kirchhoff**	*Heterogeneity of transmitter receptor induced calcium signals in astrocytes*
12:30 – 12:55	**Christian Henneberger/ Karl Martin Schwarz**	*Regional and trans-regional heterogeneity of astrocyte morphology as a functional determinant of synapse function*
13:00 – 14:00	*Lunch and Discussions*	
14:00	*End of Meeting/ Departure*	

Members of the SPP

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Poster

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Adult gliogenesis and functional astrocyte heterogeneity in the hippocampus

Yvonne Schwarz and Dieter Bruns
v-SNARE proteins in astrocytic functions and heterogeneity

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Ulrike Winkler, Susanne Köhler and Johannes Hirrlinger
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Carmen Kasakow, Laura Stopper, Gebhard Stopper, Anja Scheller and Frank Kirchhoff
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Kerstin Miebach, Christina Müller, Wen-Ping Kuo-Elsner, Martin Auber, Carsten Frühbeis, Anja Schneider, Wiebke Möbius, Anja Scheller, Laura Stopper, Frank Kirchhoff and Eva-Maria Krämer-Albers
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Camille Philippot, Lena Claus, Stephanie Griemsmann, Ronald Jabs, Christian Henneberger , Helmut Kettenmann and Christian Steinhäuser
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Rainer Pielot, Anke Müller, Frank Kirchhoff, Daniela C. Dieterich and Eckart D. Gundelfinger
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Maria Eichel, Tobias Buscham, Wiebke Möbius, Olaf Jahn and Hauke Werner
Molecular heterogeneity of CNS myelin: Novel role and regional relevance of a chemokine-like signaling protein in brain function

Abstracts:

Functional heterogeneity and dynamics of astrocytes in the adult mouse hippocampus

Ruth Beckervordersandforth
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The brain works as a functional co-operation unit between neurons and glial cells. This unit differs in its physiological properties in distinct brain regions and developmental stages. Neuronal diversity has been extensively investigated in the last decades. Recent works now suggests that also astrocytes are molecularly and functionally distinct, yet still very little is known about astrocyte heterogeneity. Most present studies focus on comparing astrocytes from different brain regions or developmental stages. However, if and to what extend astrocyte diversity within a specific region contributes to network function and plasticity has not been addressed yet. Using a genetic labeling strategy, I found that the adult hippocampal dentate gyrus is populated by morphologically distinct astrocytes that are localized to specific compartments. In sharp contrast to the prevailing assumption that astrocytes are postmitotic in the non-injured adult brain, preliminary experiments revealed proliferation of astrocytes in the adult dentate gyrus. Even more surprising was the finding that morphologically distinct astrocytes show a differential proliferation response in the context of specific stimuli (voluntary exercise and ageing). Here, I will pursue the novel hypothesis that the dentate gyrus is composed of molecularly and functionally distinct astrocytes whose dynamics are critical modulators for hippocampal adaption to changing conditions. What is the "connectome" of distinct astrocyte subtypes? Structural analysis by confocal and electron microscopy and assessment of the dynamics of astrocyte generation under distinct physiological conditions will reveal how astrocyte subtypes are embedded into the neurogenic niche and how cellular interactions and astrogenesis are modulated by physiological stimuli. What is the origin of adult generated astrocytes? In aim 2, I will investigate potential lineage relationships of astrocyte subtypes and radial glia-like neural stem cells. As structural heterogeneity of astrocytes may be a reflection of their functional properties, I aim to identify the molecular fingerprint of astrocyte subtypes by single-cell sequencing as aim 3. This data set will be used to analyse distinct molecular properties of astrocytes and to identify new markers for better targeting of astrocyte subgroups. Collectively, my studies will significantly promote our understanding of structural and molecular diversity and dynamic of astrocytes populating the same region. Furthermore, it will pave the way for selectively manipulating astrocyte subtypes in the future to address their specific functions.

v-SNARE proteins in astrocytic function and heterogeneity

Dieter Bruns and Yvonne Schwarz
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This project investigates the important role of astrocyte-neuron communication in orchestrating synaptic transmission. In the ongoing funding period, we have provided strong evidence for the co-existence of independent secretion pathways in astrocytes that employ SynaptobrevinII (SybII) and Cellubrevin (Ceb) as functionally non-overlapping v-SNARE proteins and antagonistically regulate fast glutamatergic neurotransmission. Thereby, we could elucidate new avenues of communication between astrocytes and neurons to set the stage for further experiments delineating how glio-transmission shapes neuronal signaling in vivo.

By using electrophysiological recordings in combination with high-resolution imaging and a variety of v-SNARE null mutants (constitutive and cell-type specific knock outs) as well as different Synaptotagmin deficient mice, we will investigate the activation of distinct gliotransmitter secretion pathways, their contribution to the heterogeneity of astrocyte function and participation in the context of cerebral disorders.

Regional und subregional heterogeneity of astrocytes as determinants for viscoelastic tissue properties, neuronal function and aging

Anke Müller & Daniela C. Dieterich
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In the recent years, astrocytes unravel more and more diverse and individual characteristics but in how far these heterogeneous phenotypes contribute to specific functions and particularly to a fine-tuning of neuronal activity throughout all stages of life and cognition is largely unknown.

In this proposal, we aim to extend our previous work on the investigation of molecular, cellular and regional astroglial heterogeneity by performing cell type-selective proteomic profiling of astrocytes in cocultures, acute slices and in living transgenic mice using the recently developed techniques BONCAT, FUNCAT and GINCAT. We will address the consequences of astroglial heterogeneity for synaptic plasticity at different ages in mice as well as in selected culture systems mimicking the aging brain with a special emphasis on protein translation regulation and modulation of mechanical stiffness properties by astrocytes. Furthermore, we will investigate regulation of astroglial protein synthesis as well as protein turnover depending on mechanosensitive modulation, being one candidate that might promote changes in the aging brain. For this we will use agonists and inhibitors of mechanosensitive cation channels (MSC) with a special focus on the spatial organization of protein synthesis, as well as protein turnover and local stability in astroglial microdomains with regards to astrocytic heterogeneity. Finally, we will address the effect of known rejuvenators of brain function on astrocytes and their heterogeneity in the hippocampus. Ultimately, this work shall help to understand the underpinnings of cognitive function in general as well as cognitive decline in particular.

Synaptic signal integration by NG2 cells

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Dep of [1]Neurosurgery & [2]Neuropathology, University Clinic Bonn

Thoughout lifetime myelinating oligodendrocytes of the CNS are generated and replaced by oligodendrocyte precursor cells (NG2 cells). Reecently, it has been shown that this process does not follow a rigid program and strongly depends on regional neuronal activity. Uniquely amongst glial cells, NG2 cells regularly receive hundreds of synapses from axons throughout grey and white matter of the CNS. This synaptic signaling could be key to rendering myelination of axons dependent on neuronal activity, but it has remained unclear whether NG2 cells integrate and respond to synaptic input. In the previous funding period we have shown that NG2 cells integrate strength of synaptic input in intracellular calcium levels. For this they employ various voltage-gated ion channels and use several routes of calcium entry. Within NG2 cells, Ca^{2+} signals occurred in two different spatial domains: Strong input induces global Ca^{2+} signals originating throughout the cell (proximal and distal dendrites) whereas local synaptic input can activate Ca^{2+} signals in individual dendritic segments of NG2 glial cells. Furthermore, the thin dendrites of NG2 cells represent independent electrical compartments equipped with voltage-gated K^+ and Ca^{2+} channels and acting as separate processing units of synaptic input.

In the next funding period we will across regions and age groups define the responses of NG2 cells to patterns of electrical activity of neurons, determine the responsiveness of NG2 cell dendrites to neurotransmitter and aim at describing the ultrastructure of neuron-NG2 cells synapses based on 3D correlated light and electron microscopy (CLEM FIB-feSEM). The latter shall answer the question whether the distinctness of neuron-NG2 cells synapses correlates with myelination. Finally, we employ fluorescence-based sorting of synaptosomes to explore the composition and developmental changes of neuron-NG2 cell synapses across regions and age groups

Modulation of glial diversity and functional heterogeneity concerning brain activity by the lipoprotein receptor-related protein 1 (LRP1) receptor and the glycoprotein of the extracellular matrix tenascin-C

Andreas Faissner
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We have shown with specific monoclonal antibodies such as 487^{LeX} and 5750^{LeX} that complex glycans are differentially expressed by radial glia stem cells and glial progenitors of the CNS and can be used for the sorting and enrichment of glial sub-populations. Furthermore, these Lex-glycan-variants are differentially expressed on astrocyte surfaces and thereby reveal substantial glial heterogeneity. In order to investigate potential regulatory mechanisms, we have lately characterized carrier proteins of these glycans using mass spectrometry and identified the glycoprotein of the extracellular matrix (ECM) tenascin-C and the membrane-based lipoprotein receptor-like protein-1 (LRP1) as Lex-carrier proteins. We have shown in our preliminary work that tenascin-C regulates the differentiation of astrocyte progenitors in the embryonic spinal cord. Furthermore, we have provided evidence that LRP1 partakes in the regulation of the oligodendrocyte precursor differentiation pathway. Selective ablation of LRP1 in radial glia results in severe functional deficits in the CNS of juvenile mice.

Based on these observations, we plan to investigate i) the mechanisms that mediate the effects of tenascin-C and neural ECM on astrocyte progenitor differentiation; ii) the regulation of tenascin-C and interacting extracellular matrix by Sox9, a key regulatory factor of neural stem and glial progenitor cells; iii) to study the regulation of glial differentiation and function by the receptor LRP1 by cross-breeding $LRP1^{flox/flox}$ mice with transgenic Cre-lines that target the gene in different glial lineages; iv) to investigate LRP1 and tenascin-C functions and their impact on glial diversification in stem cell niches of the adult CNS; and v) to characterize subpopulations of glial cells tagged by distinct LeX-carbohydrates further using sorting and systematic gene profiling strategies. Particular emphasis will be given to the investigation of the biological roles of glial subpopulations in the context of CNS physiology. The project is embedded in ongoing (Prof. M. Götz, Prof. Wegner) and planned collaborations (Prof. Kirchhoff, Prof. Klämbt, Prof. Steinhäuser) within the SPP 1757.

Function and mechanisms specifying the heterogeneity of forebrain astrocytes

Magdalena Götz,
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In the previous funding period we identified intriguing differences between parenchymal astrocytes from the cerebral cortex grey matter and the diencephalon. Most importantly we showed that diencephalic astrocytes proliferate in vivo and have neural stem cell hallmarks in vitro as they form multipotent and self-renewing neurospheres. Thus we have identified a novel neural stem cell niche in the adult brain and propose a novel concept of region-specific astrocytogenesis in vivo. In addition we identified a key regulator of these region-specific hallmarks of diencephalic astrocytes, Smad4. Inducible Smad4 deletion in astrocytes shows a selective reduction in astrocyte number in the diencephalon, but not the cerebral cortex, as well as a severe reduction in the neurosphere forming capacity of diencephalic astrocytes.

In the first part of the project proposed for the coming funding period we would like to examine and understand the role of the ongoing astrocytogenesis in the adult diencephalon. This will be done by clonal analysis to determine the extent of astrocyte addition or turnover, as well electrophysiological recordings of proliferating astrocytes in the diencephalon to determine their functional properties and potential influences on the network properties. We will also perform behavior analysis of the Smad4 mutant mice as an entry point to understand the effects of reduced astrocytogenesis in the diencephalon. In the second part of the project we aim to understand to which extent the region-specific differences of diencephalic and cortical astrocytes depend on their location, i.e. extrinsic factors, or are intrinsically determined. Towards this end, we will transplant astrocytes from the cerebral cortex into the diencephalon to determine if the diencephalon environment is sufficient to elicit proliferation and neurosphere formation in astrocytes from the cerebral cortex. As Smad4 is a mediator of extrinsic or intrinsic mechanisms specifying diencephalic astrocyte hallmarks, we aim to identify its transcriptional targets that mediate these hallmarks of diencephalic astrocytes by RNA-seq and ChIP seq.

Regional and trans-regional heterogeneity of astrocyte morphology as a functional determinant of synaptic astrocyte-neuron interactions in the hippocampus

Christian Henneberger & Karl-Martin Schwarz
Rheinische Friedrich-Wilhelms-University Bonn, Institute of Cellular Neurosciences

Synaptic transmission and its plasticity are modulated by fast reciprocal signal exchange between neurons and astrocytes on the synaptic level. This astrocyte-neuron signalling often involves diffusible signals. Therefore, its efficiency is likely to depend on the spatial proximity between neuronal structures and perisynaptic astrocyte processes and thus on astrocyte morphology. As a consequence, the heterogeneity of astrocyte morphology should have important implications for synaptic transmission. Indeed, we could demonstrate that the structural heterogeneity of astrocytes in the rodent CA1 *stratum radiatum* has important consequences for presynaptic release at the CA3-CA1 synapse, a standard model system in cellular neurophysiology. Using combinations of two-photon excitation fluorescence microscopy and novel electrophysiological approaches we could reveal that variations of the structural complexity of astrocytes determines presynaptic short-term plasticity via astrocytic glutamate receptors, likely through differential coverage of synapses by astrocyte processes. In this project, we will now build on this finding by first uncovering how regional intercellular heterogeneity of astrocyte morphology determines the local coverage of glutamatergic CA3-CA1 synapses and also GABAergic connections. To this end, we have established expansion microscopy (ExM, Chen et al. 2015, Chozinski et al. 2016). ExM enables us to super-resolve the structural relationship between synapses and perisynaptic astrocyte structures, which cannot be fully visualized by diffraction-limited microscopy. Second, we will extend our investigation to adjacent layers of the CA1 region, where astrocytes display different morphologies and cover other dendritic domains of the same CA1 pyramidal cell neurons and their incoming excitatory connections. By combining imaging and electrophysiological techniques with ExM we will reveal how trans-regional heterogeneity of astrocyte morphology determines the local properties of excitatory synapses received by a single neuronal cell type. Third, we will establish how astrocyte morphology and its intercellular and subcellular specialisation determines the responsiveness of astrocyte to synaptic activity. Here we will focus on how the proximity of astrocyte processes to glutamatergic synapses determines the likelihood that a synaptic stimulus results in a local astrocytic Ca2+ transients and how it affects their magnitude and underlying signalling cascades. These functional experiments will again be supported by structural analysis using ExM. Fourth, we will explore the relationship between astrocyte structure, its heterogeneity and synaptic astrocyte-neuron interactions in human tissue samples. In summary, we will establish how regional and trans-regional structural heterogeneity and specialisation of astrocytes determine local synaptic coverage by astrocyte processes and the functional relevance for astrocyte-neuron interactions.

Metabolic heterogeneity of astrocytes in grey and white matter of the brain

Johannes Hirrlinger
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Astrocytes crucially contribute to brain energy metabolism. However, the environment and therefore the requirements for these cells are very different in grey and white matter. Astrocytes in grey matter mainly contact synapses, blood vessels and other astrocytes, while white matter astrocytes mainly contact axons (at the node of Ranvier), oligodendrocytes and their myelin. Functionally, the major task for neurons within grey matter is transmission and computation of information at synapses; white matter tracts are specialized to allow reliable axon potential propagation along axons for long distances. We hypothesize that these diverse environments and requirements result in metabolic heterogeneity of astrocytes in respect to different basal as well as stimulated energy metabolism including regulation by different signals. In addition, we hypothesize that metabolic feedback to signaling is different in these cells. Therefore, this project aims at unraveling the discriminative metabolic events in astrocytes of grey and white matter, the underlying regulatory principles as well as their physiological relevance for brain function. These objectives will be addressed using state-of-the-art methodology including imaging of metabolites employing genetically encoded fluorescent sensors and calcium imaging in acutely isolated brain slices from mice comparing cortex and corpus callosum. Mechanisms underlying metabolic differences between astrocytes in grey and white matter will be established using cell transplantations between different brain regions as well as by correlation of metabolic phenotypes with gene expression profiles. We expect to identify differences between astrocytes in grey and white matter in basal energy metabolism as well as in the main regulatory mechanisms affecting astrocytic energy metabolism, but also providing feedback from metabolism to signaling events. In addition, we expect obtaining insights on how the astrocytic metabolic phenotype is specified in different areas of the brain. In summary, the proposed project aims at establishing a comprehensive picture of astrocytic metabolism, its regulation, and heterogeneity in different but also within brain regions. These insights will allow a deeper understanding of how brain energy metabolism is embedded in brain physiology to enable brain function.

Heterogeneity of transmitter receptor induced Ca^{2+} signals in astrocytes

Frank Kirchhoff
Molecular Physiology, CIPMM, University of Saarland, Homburg/Saar

Astrocytes represent a main cell population in the central nervous system. Although they are electrically non-excitable, they display a complex spatial and temporal pattern of Ca^{2+} signals. The complexity is not only restricted to the intracellular distribution, but varies also among adjacent astrocytes or astrocyte subpopulation. Here, we will study the modulation of these Ca2+ signals by astrocyte-expressed receptors that are responsive to a range of excitatory, inhibitory and modulatory transmitters. Inducible and astrocyte-specific gene recombination in combination with in vivo two-photon laser-scanning microscopy and electrophysiology will be employed to study the impact of the purinergic receptor subunit P2Y1, the NMDA-type glutamate receptor NR1, the GABAB receptor GBR1 and the adenosine A1 receptor on mouse brain function and behavior.

Impact and regional aspects of glia to neuron exosome transfer in the CNS

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Institute of Developmental Biology and Neurobiology (IDN), Molecular Cell Biology, Johannes Gutenberg University Mainz

Oligodendrocytes myelinate axons and in addition maintain axonal integrity by providing support to neurons. We have shown that oligodendrocytes secrete nano-sized vesicles termed exosomes, which mediate bidirectional neuron-glia communication. However, their impact on brain physiology is largely unresolved. Exosomes are released by oligodendrocytes upon neurotransmitter signalling and internalized by neurons via endocytosis delivering a variety of biomolecules, including RNA, from oligodendrocytes to neurons. Cultured neurons that have received exosomes are more resilient to stress suggesting that oligodendroglial exosomes mediate neuroprotection. Modification of exosomes to carry reporter enzymes such as Cre recombinase is utilized to illustrate transfer of exosomes and their cargo to target neurons allowing the identification of target neurons in the brain.

In this project, we aim to determine the brain regions, where exosome transfer from oligodendrocytes to neurons is prevalent, and the specific neuronal subpopulations targeted by exosomes. Our strategy utilizes tamoxifen-inducible CreERT2-mediated recombination of target cells to trace exosome transfer in the brain of reporter mice. In addition, the coupling of exosome transfer to neural electrical activity will be assessed. Exosome transfer from NG2-cells to neurons and mature oligodendrocytes to neurons will be compared regarding their targeting characteristics revealing potentially distinct functional implications. Furthermore, we will determine the influence of glial exosomes on the transcriptomic profile of target neurons. The aim is to reveal deeper insight into the prevalence of exosome-dependent neuron-glia communication in distinct brain regions and its functional relevance for neural performance and plasticity.

Visualizing glial support of axon function with metabolic sensors in transgenic mice

Klaus-Armin Nave
Department of Neurogenetics, Max-Planck-Institute for Experimental Medicine, Göttingen, Germany

In white matter, axonal energy homeostasis critically depends on oligodendroglial support. Failure in glial-mediated delivery of metabolic substrates into the axonal compartment results in axonal energy deficit and may anticipate the axonal degeneration observed in myelin disorders and several neurodegenerative diseases. In mice, the transgenic expression of an ATP-sensor in neurons allowed us to visualize axonal energy content in acutely isolated optic nerves while simultaneously performing electrophysiological compound action potentials (CAP) recordings. The real-time monitoring of activity-dependent axonal ATP revealed a strong correlation between axonal energy fluctuations and nerve conduction. Importantly, upon pharmacological inhibition of endogenous lactate metabolism while under continuous glucose supply, ATP-CAP correlation was disrupted, suggesting that the axonal glycolysis products alone are insufficient to maintain axonal mitochondrial energy metabolism during spiking activity. To determine possible metabolic consequences of myelin defects we monitored ATP and CAP in *Plp1*-null optic nerves. Genetic ablation of *Plp1*, encoding a myelin membrane protein, serves as a model of spastic paraplegia type-2, where functional but structurally destabilized myelin sheaths lead to secondary axonal loss. We found that the energy metabolism of myelinated axons of *Plp1*-null optic nerves is perturbed long before the onset of clinical symptoms and major pathological changes. These observations motivated us to also assess the metabolic properties of spinal cord fibres in vivo and under the acute and chronic stress of myelin disease. We are aiming further at investigating the metabolic crosstalk between axons and glial cells, and the role of lactate as fuel for axonal ATP production *in vivo*. To achieve this, we are making use of a chronic window in the spinal cord of reporter mice, which allows for repetitive ATP and lactate imaging during different phases of myelin disease and functional recovery

Functional heterogeneity of ependymoglial cells in adult zebrafish telencephalon

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Lehrstuhl Physiologische Genomik; Biomedizinisches Zentrum
Ludwig-Maximilians-Universität (LMU) München

The ependymoglial cells in the zebrafish telencephalon act as adult neural stem cells, but also serve the supporting role of mammalian protoplasmic astrocytes and ependyma such as metabolic support, synapse enwrapping, etc. At present it is not clear if the same cell has both functions or if different populations provide different functions. We have prospectively isolated two ependymoglial populations and compared their transcriptomes. The transcriptome analysis suggests that one population could provide new neurons (neurogenic ependymoglia), while the other has the characteristics of the bone fide protoplasmic astrocytes (gliogenic ependymoglia). Within this grant, we will further characterize these two populations using the transcriptome and metabolic analysis. We will perform the genetic fate mapping of these two populations addressing their potential in the intact fish brain and assess their functional importance using the ablation experiments. Finally, we will address the origin of the two populations during the development and assess the molecular pathways specifying these two ependymoglial populations. Within this proposal, we will utilize the unique feature of the zebrafish telencephalon, the coexistence of the bona fide glial cells and stem cells in the same niche, to infer the emergence of neural lineages in vertebrates and provide the molecular and cellular basis for the further analysis in mammals.

Heterogeneity in astrocyte sodium signalling: Functional consequences

Christine R. Rose
Institute Neurobiology, Heinrich Heine University Düsseldorf

Earlier work performed in juvenile mouse hippocampus and cerebellum has established that astrocytes respond to excitatory synaptic activity with transient increases in their sodium concentration, which are mainly generated by high-affinity glutamate uptake. Changes in astrocyte sodium are functionally highly relevant because they alter the activity of sodium-dependent transporters such as the sodium/calcium exchanger (NCX) and serve an important role in neuro-metabolic coupling. In the first funding period of the SPP, we revealed the existence of developmental, subcellular and inter-regional heterogeneity in astrocyte sodium signalling in the mouse brain. In this context, we uncovered marked differences in the magnitude and pathways of sodium signals between neocortex and hippocampal CA1 region. Cortical astrocytes not only respond with much larger sodium transients to glutamate and to activation of glutamatergic afferents, they also experience strong NMDA-receptor-mediated sodium influx, a component, which hippocampal astrocytes lack.

In the second funding period, we now aim to address the possible functional consequences of this heterogeneity. Employing high-resolution, fluorescence-based imaging of ion transients in combination with whole-cell patch-clamp and genetically-encoded nanosensors for metabolites, we will test the hypothesis that activity-induced astrocyte sodium transients are coupled to intracellular calcium homeostasis and signalling through NCX. Furthermore, we propose that they directly influence glial metabolism. The striking difference in the magnitude of activity-related astrocyte sodium signals between hippocampus and neocortex suggests functional differences between both brain regions. We hypothesize that this inter-regional functional heterogeneity of astrocytes mainly relates to the heterogeneity in sodium influx through NMDA receptors. Finally, we propose that differential sodium signalling -as mediated by NMDA receptors- amplifies sodium-related calcium signalling and augments neuro-metabolic coupling in neocortical as compared to hippocampal networks.

Transcriptomic profiling and integrated bioinformatic analyses of glial cell types of the brain

Moritz Rossner
Department of Psychiatry, Molecular Neurobiology, LMU Munich

Increasing evidence suggest that glial cell type heterogeneity contributes to higher order brain functions. Astroglial cells, for example, are essential in modulate in synaptogenesis during development and maintaining the metabolic integrity of neurons in the mature brain. In the proposed project and with several partners of the SPP1757, we aim at applying deep sequencing of MACS, FACS and RiboTag purified glial cell populations from different brain regions and developmental stages to generate a comprehensive molecular catalogue of glia. In depth bioinformatic analyses and visualizations will be used to setup a database for follow up queries and public accessibility. By analyzing the transcriptomes of cortical astrocytes harvested at early postnatal developmental stages, we identified several astrocyte expressed genes which have been implicated in synaptogenesis and metabolic support. For most of these developmentally regulated genes, however, the function is not known. We will apply a combined bioinformatic guided selection and experimental validation screen to identify novel astrocyte expressed genes and mechanisms which modulate neuronal activity during development and in the adult brain

In vivo responses in CNS glia to peripheral metabolic changes

Gesine Saher
Department of Neurogenetics, Max-Planck-Institute of Experimental Medicine, Göttingen

Integrity of the complex brain functions relies on import, utilization and excretion of appropriate metabolites. While glucose maintains neural metabolism under physiological conditions in the adult animal, 60-70% of the brain energy demand can be met by ketone bodies (KB) in case of starvation, dietary intervention with ketogenic diets (fat is main energy source) or during the suckling period of mammals as a natural condition of ketosis. During ketosis, the liver catabolizes fat to produce KB, predominantly beta-hydroxybutyrate and acetoacetate. Monocarboxylate transporter 1 (MCT1) which is abundantly expressed in endothelial cells of the blood-brain barrier during the first weeks of postnatal development, facilitates the entry of KB into the brain. When mice are weaned, glucose becomes the major energy source for brain cells concomitantly with a change in expression of respective transporters; MCT1 is downregulated, while the glucose transporter GLUT1 is upregulated. Also brain metabolism switches, downregulating ketone body utilization and upregulating glucose utilizing enzymes.

While these global changes have been characterized in considerable detail, it is unknown how brain cells, especially astrocytes and oligodendroglial cells adapt to the metabolic switch to facilitate brain development. What is the cell type specific metabolic specialization? What is the metabolic crosstalk between these glial cells and neurons in the developing brain? In this proposal we compare mice that are reared on ketogenic diet with normally reared mice. We aim at integrating cell type specific profiling data obtained by in vivo sampling of non-diseased CNS glia. We anticipate that our findings will contribute to the understanding of the metabolic heterogeneity of glial subtypes and shed light on the metabolic coupling between neural cells to maintain functional integrity which might open new roads for managing neurodegenerative pathologies.

Impact of AMPA receptors and Kir4.1 channels in grey matter NG2 glia on myelination, signal transmission and behaviour: Comparative studies in the hippocampus and cerebellum

Gerald Seifert & Christian Steinhäuser
Institute of Cellular Neurosciences, University of Bonn

The physiological impact of neuron-NG2 glia synapses in grey matter is unclear. Specifically, it remains unknown under which conditions and through which mechanisms synaptically activated NG2 glia feed back to neurons. Grey matter NG2 glia display heterogeneous properties. For example, stimulus-induced postsynaptic responses of NG2 glia in the cerebellum exceed those in hippocampal NG2 cells more than 10fold. Cause and consequence of this functional diversity are not known. To investigate presumed NG2 glia-neuron back signalling and NG2 glia heterogeneity, we have generated mice with inducible NG2 cell-directed genetic deletion of AMPA receptors (quadruple GluA flox mice) and Kir4.1 channels (Kir4.1 flox mice). In the previous funding period we have found that these mice display altered myelination and synaptic plasticity. In addition we have found brain region-specific differences in the expression of auxiliary AMPA receptor subunits, which might confer higher efficiency on neuron-NG2 glia synapses in the cerebellum. In our follow-up proposal we will build on these findings and address the following questions:

i) Does heterogeneous expression of AMPA receptors or auxiliary subunits contribute to the stronger responsiveness to synaptic activation of cerebellar vs. hippocampal NG2 glia? Ca2+ permeability and kinetics of GluA subunits and auxiliary subunits critically influence the efficiency of synaptic transmission. We will determine whether differences in receptor splicing and presence of the auxiliary subunit TARP gamma-2 contribute to the higher and variable responsiveness of cerebellar NG2 glia to synaptic stimulation.

ii) What is the impact of AMPA receptors in hippocampal and cerebellar NG2 glia: Do synaptically activated NG2 glia signal back to neurons and influence behaviour? We will characterize on the cellular, network and behavioural level the consequences of NG2 glia-targeted deletion of AMPA receptors, to deduce their physiological impact.

iii) Do Kir4.1 channels in NG2 glia influence the efficiency of their synaptic input, back signaling to neurons and behaviour? Kir4.1 flox mice display enhanced myelination and impaired neuronal plasticity. We will identify the molecular mechanism(s) underlying these alterations and investigate its behavioural consequences.

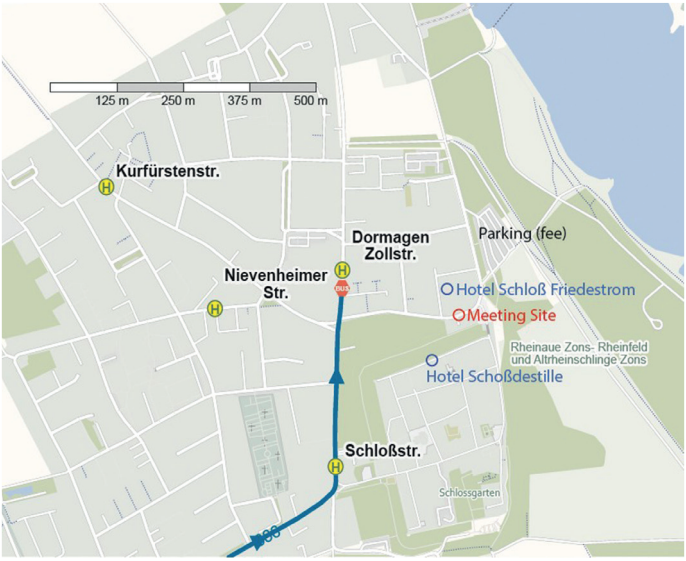
Molecular heterogeneity of oligodendrocytes: novel role and regional relevance of a chemokine-like signaling protein in brain function

Hauke Werner
Max Planck Institute of Experimental Medicine, Göttingen

CNS myelin is provided by mature oligodendrocytes, which display regional heterogeneity with respect to morphology and electrophysiological properties. However, underlying molecular-genetic diversity has not been reported. We hypothesized that regional oligodendrocytic heterogeneity is reflected at the molecular level in the protein composition of myelin. In pilot experiments, we have used quantitative mass spectrometry to determine the proteome of myelin purified from various regions of healthy mouse brains. While the abundance of major structural myelin proteins, such as PLP or MOG, is largely similar across the analyzed brain regions, several non-structural proteins display considerable heterogeneity of abundance, e.g. in myelin from the cortical gray matter compared to the subcortical white matter. To select proteins for more detailed analysis, we have evaluated our datasets for heterogeneously abundant myelin proteins with a probable function in cellular metabolism or intercellular signaling. In a pilot experiment, we identified CMTM5 (*chemokine-like factor MARVEL transmembrane-domain containing protein 5*) and genetically deleted its expression specifically in oligodendrocytes. Based on our unpublished observations we will test the hypothesis that CMTM5 is not involved in the biogenesis of myelin *per se* but in oligodendrocytic signaling to myelinated axons. This project will involve biochemistry/proteomics, mouse genetics, electron microscopy and assessment of mouse behaviour. We anticipate that signaling proteins such as CMTM5 contribute to establishing regionally distinct functions of oligodendrocytes; this novel concept will be tested *in vivo*.

How to get to the meeting site

Parkstraße 2, 41541 Dormagen
51.123149 | 6.850619



Travel information
We suggest using the Rheinbahn's timetable for the quickest way to reach your goal:
Next train station: Dormagen Bahnhof
Next bus stop: Dormagen Zollstrasse

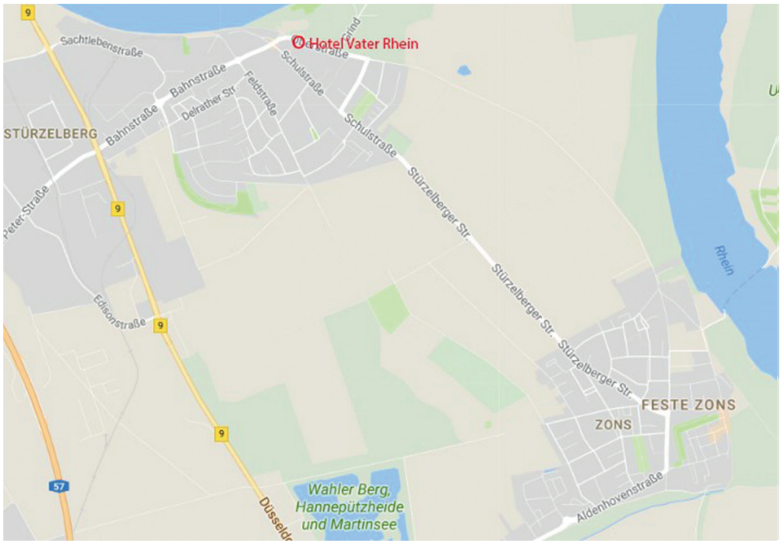
Arriving by train
Düsseldorf and Cologne main stations are connected to all international long-distance train routes. From there, take a direct train to Dormagen Bahnhof and then take the bus 875, 886 or 887 to Zons, Zollstrasse.

Arriving by plane
Düsseldorf Rhine-Ruhr (DUS) and Cologne – Bonn (CGN) airports are both good options. From both airports there are direct connections to Dormagen station by city train (S-Bahn S11 from DUS) and by regional fast train (RE6 from CGN and DUS).
From Dormagen station proceed as described above or take a taxi (10-15 EUR.).
It might be a good idea to call taxi companies in advance (Taxi Hillmann: 02133 3333, Taxi Surmann: 02133 44444 or Mietwagen Uschi 02133 978897).

Where to stay

Hotel Friedestrom, Parkstr. 2, Zons, Fon 02133 5030, info@friedestrom.de. meeting site (see map of meeting site)
Hotel Schlossdestille. Mauerstr. 26a, Zons, Fon 02133/47658, info@schlossdestille.de, 2 min walk from the meeting site within the old town. (see map of meeting site, see separate instruction of how to get there by car)
Hotel Vater Rhein, Oberstr. 4, Stürzelberg, Fon: 02133/71930, info@gasthof-vaterrhein.de. **Attention: The reception is closed between 12:00 and 15:00!** Busstop: Unterstr., Buses 875, 886 or 887, Direction Nievenheim or Neuss. It is a 5 min bus ride. see map below

We asked Hotels Friedestrom and Schlossdestille for early check-in (from 12.00 o'clock on). They will try, but cannot guarantee for all of the rooms.



Parking

The Hotel Friedestrom has a few parking lots which are for free.
The big parking ground nearby costs 3 Euro per day. Take care, they will charge you 60 Euros if you don't pay the fee!
West of Deichstraße parking in most streets is for free. But take care at the REWE parking ground. There, only one hour is for free. A company is controlling that and they'll fine you if you park for longer.

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