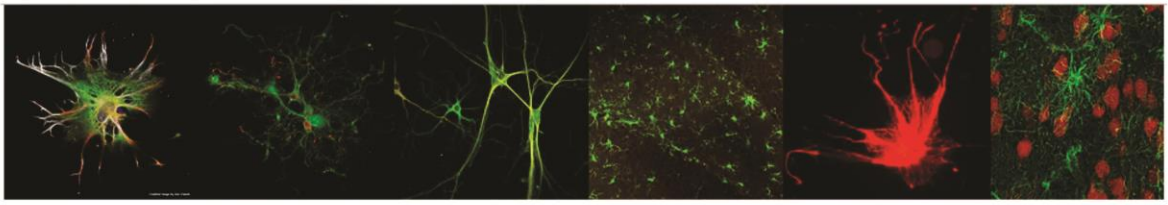

Functions of Neuroglia

International Conference

September 26-28, 2019, Tbilisi, Georgia

Functions of Neuroglia

International Conference

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In commemorial of
Alexander Roitbak's
100th birthday

Abstracts

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Speaker Presentation Abstracts

Oligodendrocyte dynamics in the adult brain

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Myelination patterns in the cerebral cortex are highly variable, with sheath content varying among different types of neurons and even along the length of individual axons. Despite this evidence of discontinuous myelination, our recent in vivo imaging studies indicate that myelin sheaths in the adult CNS are remarkably stable, suggesting that maintaining sheath placement is important for cortical function. The destruction and regeneration of myelin sheaths in the cortex is a critical component of multiple sclerosis (MS) pathogenesis. In both relapsing-remitting forms of human MS, and the cuprizone model of demyelination in mouse, the cortex is capable of spontaneous remyelination. However, it is unknown whether precise myelination patterns are restored following oligodendrocyte regeneration.
To determine the specificity of myelin repair in the cortex, we performed longitudinal in vivo two-photon microscopy to follow individual oligodendrocytes and their myelin sheaths through de- and remyelination in MOBP-EGFP mice fed 0.2% cuprizone diet for 3 weeks. This protocol was sufficient to induce near-complete loss of oligodendrocytes within the upper layers of cortex, with complete restoration of oligodendrocytes occurring after 5 weeks. However, deeper layers of the cortex failed to regenerate as robustly, only reaching ~60% of control density by 9 weeks. Regenerated oligodendrocytes were formed in different locations, but had similar overall morphologies and comparable sheath production, despite the larger axonal territory available, suggesting oligodendrocyte size is primarily determined by cell autonomous mechanisms. Unexpectedly, myelin sheaths from regenerated oligodendrocytes overlapped only weakly with the territories of previous oligodendrocytes, and less than a randomly distributed population, suggesting that inhibitory factors may prevent regenerated oligodendrocytes from differentiating within the territories of degenerated cells. As a result, only 58% of individual myelin sheaths were restored and many novel sheaths were formed along previously-unmyelinated axon segments. However, for instances where sheaths were replaced, their placement along axons was remarkably conserved, suggesting that molecular marks that dictate sheath location are maintained along demyelinated axons for many weeks. These studies suggest that despite efficient oligodendrocyte regeneration, overall myelination patterns are not preserved during remyelination, which may have consequences for sensory processing and cognitive function.

Identifying novel targets to promote life-long generation of oligodendrocytes and myelin

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The massive computing power of the brain depends on myelinated fibres that are bundled together into the white matter (WM) to form 'superhighways of information' that interconnect widely dispersed neuronal networks. Myelin is produced by oligodendrocytes, specialised glial cells that are derived from oligodendrocyte precursor cells (OPCs). Notably, there is life-long generation of oligodendrocytes from OPCs, which is required for replacement of myelin lost through natural 'wear and tear', for myelination of new neuronal circuits formed in response to new life experiences and, crucially, regeneration of oligodendrocytes following pathological demyelination, such as occurs in multiple sclerosis. However, the factors that regulate OPC regeneration and how these are altered in the ageing brain are unresolved. We show the regenerative capacity of OPs decreases with age and there is associated myelin loss and cognitive decline in the ageing brain. Notably, our evidence indicates a central role for deregulation of neurotransmission and Wnt signalling in compromised oligodendrogenesis. Furthermore, we have used a pharmacogenetic approach to identify novel drug targets to promote rejuvenation of oligodendrogenesis. In summary, our studies identify new targets to promote the life-long generation of oligodendrocytes, which is critical for healthy brain function.

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The identity and function of microglia in neurodegeneration

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The predominant type of immune cell in the brain is the microglia, a type of tissue-resident macrophage. In a variety of neurodegenerative settings, microglia alter their transcriptional profile, morphology and function in similar ways; thus, these activated cells have been called 'degeneration- or disease-associated microglia' (DAM). These activated microglia can perform different functions and exert both positive effects and negative effects in different mouse disease models. In humans, mutations in genes expressed in microglia are linked to various neurodegenerative diseases. I will provide an overview of the common microglial response to neurodegeneration and key contributing pathways; delineate the multifaceted functions of activated microglia spanning various diseases; and discuss insights from the study of human disease-associated genes. I argue that strong evidence from both mouse models and human genetics causally links the function of activated microglia to neurodegeneration.

Motor-Skill Learning and Astroglial Plasticity

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Astrocytes, a type of glial cells, perform multiple tasks in the brain and have been implicated in regulating synaptic development, function and plasticity. Astrocytes display activity-mediated Ca2+ responses and Ca2+ signaling in astrocytes is thought to be involved in astrocyte-neuron signaling. Here we investigated astrocyte Ca2+ signaling in the primary motor cortex during movement and with motor skill learning. We performed in vivo multiphoton imaging in the primary motor cortex of awake head-fixed mice, expressing genetically encoded Ca2+ indicator GCaMP6f in astrocytes, while engaged in different behaviors in a mobile home cage. We found astrocyte Ca2+ activity is increased in the primary motor cortex during movement as well as during the pre-movement planning period. We also trained mice on a forelimb-reaching task, a motor skill learning paradigm which is known to modulate synaptic structure and function in the primary motor cortex. We first asked whether astrocyte Ca2+ signaling is necessary for learning and found that pharmacologic or genetic (IP3R2 KO mouse) blockade of astrocytic Ca2+ signaling impairs motor learning as well as synaptic plasticity. We next asked if motor skill learning modulates astrocyte Ca2+ signaling and show for the first time that in addition to enhancing synaptic strength, motor skill training results in enhanced frequency and amplitude of astrocyte Ca2+ transients in the primary motor cortex. In ongoing studies, we investigate if altered astrocyte Ca2+ signaling contributes to the pathogenesis of Fragile X Syndrome, a neurodevelopmental disorder, using mouse models and patient derived induced pluripotent stem cells.

Involvement of Astrocytes and Oligodendrocytes in Tau Seeding and Spreading in Tauopathies

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Human tau seeding and spreading occur following intracerebral inoculation of brain homogenates obtained from tauopathies in transgenic mice expressing wild or mutant tau, and in wild-type mice.
The present study is geared to learning about the patterns of tau seeding, the cells involved, and the characteristics of tau following intracerebral inoculation of homogenates from primary age-related tauopathy (PART: neuronal 4Rtau and 3Rtau), pure aging-related tau astrogliopathy (ARTAG: astroglial 4Rtau with thorn-shaped astrocytes TSAs), globular glial tauopathy (GGT: 4Rtau with neuronal tau and specific tau inclusions in astrocytes and oligodendrocytes, GAIs and GOIs, respectively), progressive supranuclear palsy (PSP: 4Rtau with neuronal inclusions, tufted astrocytes and coiled bodies), Pick's disease (PiD: 3Rtau with characteristic Pick bodies in neurons and tau containing fibrillary astrocytes), and frontotemporal lobar degeneration linked to P301L mutation (FTLD-P301L: 4R familial tauopathy).
Young and adult WT mice were inoculated in the hippocampus or the lateral corpus callosum with sarkosyl-insoluble fractions and sarkosyl-soluble fractions from tauopathies, and were killed at variable periods of from three to seven months. Brains were processed for immunohistochemistry in paraffin sections.
Tau seeding occurred in the ipsilateral hippocampus and corpus callosum, and spread to the septal nuclei and contralateral corpus callosum. Tau deposits were found mainly in neurons and oligodendrocytes, and in threads which contained phosphorylated tau, tau with abnormal conformation, and 3Rtau and 4Rtau independently of the type of tauopathy, but not truncated tau at aspartic acid 421. Moreover, tau deposits co-localized with active (phosphorylated) tau kinases p38 and ERK½, indicating active tau phosphorylation of murine tau.
Seeding and spreading of human tau in the brain of WT mice involves neurons and glial cells, mainly oligodendrocytes, thereby supporting the idea of a primary role of oligodendrogliopathy in the progression of tauopathies. This process is particularly important in the white matter, which acts as a corridor of tau seeding and spreading in tauopathies. Human tau inoculation modifies murine tau metabolism with the production and deposition of 3Rtau and 4Rtau, and by activation of specific tau kinases in affected cells.

Astrocytes Regulate Myelin Structure to Adjust Spike Time Arrival for Optimal Neural Circuit Performance

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Optimal neural circuit function and plasticity require the proper impulse transmission speed through all axons, for temporal summation at synapses, spike-timing-dependent plasticity, and sustaining oscillations at appropriate frequencies. Psychological and neurological dysfunctions can develop when optimal synchrony of spike time arrival is disturbed. Mechanisms that modify conduction time through axons could provide a non-synaptic mechanism of neural circuit plasticity. Conduction velocity through myelinated axons is highly dependent on the thickness of the myelin sheath and morphology of the electrogenic nodes of Ranvier along axons. Myelination of unmyelinated axons and the thickness of the myelin sheath can be increased in response to neural activity, environmental experience, and during growth of axons, but is unknown whether the thickness of the mature myelin sheath can be thinned to adjust conduction velocity to obtain optimal spike time arrival. Our research indicates that myelin thickness and morphology of the node of Ranvier can be regulated dynamically by proteolysis of cell adhesion molecules attaching myelin to the axon in the paranodal region, and that this plasticity is under control of perinodal astrocytes. Experiments on the visual system of mice show that these structural changes modify conduction velocity for optimal function, suggesting myelin plasticity as a new form of nervous system plasticity.

How are nervous systems remodeled in complex metazoans?

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Early in development, the nervous system is constructed with far too many neurons that make an excessive number of synaptic connections. Later, a wave of neuronal "remodeling" radically reshapes nervous system wiring and cell numbers through the selective elimination of excess synapses, axons and dendrites, and even whole neurons. This type of neuronal remodeling is widespread across the nervous system, extensive in terms of how much individual brain regions can change (e.g. in some cases 50% of neurons integrated into a brain circuit are eliminated), and thought to be essential for the construction of a nervous system that is optimized, and properly functioning. Remodeling requires intrinsic neuronal pathways, but also neuron-glia signaling events, which have only recently been appreciated, and neither of which are well understood. Perturbations of neuronal remodeling are thought to underlie devastating neurodevelopmental disorders including autism spectrum disorder, schizophrenia, and epilepsy, so there is a pressing need to transform our approach to studying neuronal remodeling and our understanding of its cellular and molecular features.

Why do we understand so little about developmental remodeling? Relative to other aspects of nervous system development (e.g. axon pathfinding, cell fate specification), it has been understudied. More importantly, neuronal remodeling has only been explored in a very limited number of lineages in any organism. Our knowledge comes from a handful of lineages in mouse or Drosophila, and a survey of these models quickly reveals that they each exhibit a unique cellular type of remodeling (e.g. cell death versus axon, dendrite, or synaptic pruning) and they activate and execute remodeling through unique molecular programs. Given that neuronal remodeling has only been studied in a very small number of neuronal cell types (especially in vivo), and they all appear to drive remodeling differently, it seems likely that we have only scratched the surface of the mechanistic basis of neuronal remodeling. We have ignored ~95% of the cells in the mammalian nervous system. We are exploiting a collection of new tools, reagents we have assembled for studying neuronal remodeling, and the panoply of powerful molecular-genetic approaches available in Drosophila to perform a comprehensive study of neuronal remodeling. Our goal is to identify markers for the vast majority of cellular and molecular subtypes of pruning that occur throughout in the Drosophila brain. After classifying lineages based on their cellular patterns of remodeling and molecular features, we will select a handful of lineages to use to identify neuron-intrinsic signaling pathways that drive activation and execution of neuronal remodeling, and signaling pathways mediating neuron-glia interactions. Surprisingly, even in Drosophila, no lineages have been directly targeted by forward genetic approaches (e.g. EMS loss of function mutant screens), so a wealth of exciting new genes regulating neuronal remodeling await discovery. Our work holds promise to define the basic cellular and molecular principles that dictate patterns of neuronal remodeling, generate a battery new tools that will allow for deep mechanistic studies of a diversity of types of pruning events, and our characterization of novel pruning mechanisms will provide much-needed targets for therapeutic intervention in neurodevelopmental and neurodegenerative disorders.

Nature and nurture of human microglia

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Microglia play essential roles in central nervous system (CNS) homeostasis and influence diverse aspects of neuronal function. Although dysregulation of microglia activity is genetically linked to neurodegenerative and psychiatric diseases, the transcriptional mechanisms that specify human microglia phenotypes are largely unknown. We characterized the transcriptomes and epigenetic landscapes of human microglia isolated from surgically resected brain tissue, revealing that genes associated with risk alleles or exhibiting altered expression in neurodegenerative diseases are preferentially or highly expressed in human microglia in comparison to intact brain tissue. The transition of human and mouse microglia from the brain to a tissue culture environment results in rapid and extensive downregulation of genes, identifying sets of environmentally sensitive transcripts. These findings provide the basis for a working model of an environment-dependent transcriptional network specifying the microglial gene expression program. In current efforts, we are developing methods for investigation of transcriptional networks and epigenetic landscapes of human microglia, astrocytes, oligodendrocytes and neurons in the context of neurodegenerative diseases. These studies are providing improved interpretation of non-coding genetic variation that is associated with risk of Alzheimer's disease and other neurodegenerative disorders.

Reactive glia as a trigger of synapse dysfunction and cognitive impairment

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When growing older, people are often confronted with mild cognitive impairments. These may progress into dementia, as observed in Alzheimer's disease (AD). In case of AD this process is triggered by oligomeric forms of Abeta protein which induce chronic reactive astrocytes and activated microglia, and negatively affect synapses leading to the initial cognitive impairments that might later develop into a full dementia.
Glial cells are essential in regulating optimal neuronal communication and synaptic transmission. Astrocytes form an intricate part of the synapse and microglia may prune inactive synapses. Whole genome-wide analysis of acutely isolated glia from aged and AD mice revealed that aged astrocytes and microglia have a more immune activated phenotype and that the neuron-support function of AD astrocytes is declined. We also observed that reactive glia in AD have an increased expression of immunoproteasome subunits, resulting in an increase in immunoproteasome activity in AD brains.
Our earlier data showed that chronically activated astrocytes lose their neuron support function, ultimately interfering with synaptic efficacy. We observed a clear decrease of Kir mRNA at the molecular level, and therefore we studied astrocyte Kir channel dysfunction in AD. In contrast with the mRNA findings, we found that Kir4.1 protein expression in the hippocampus of AD mice was increased in astrocytes surrounding amyloid plaque deposits. Our results suggest that astrocytes in the AD mice are resilient in their K+ clearance mechanism and attempt to rectify imbalances in K+ concentration to restore normal neuronal and synaptic function, possibly by redistribution of K+ through Kir channels. In addition, we observed increased spontaneous calcium transients in hippocampal AD astrocytes that were also longer in duration.
There is growing evidence that glia are centrally involved in many neurological diseases. In addition, the molecular and cellular mechanisms underlying cognitive impairment might be similar in different diseases. Studying these mechanisms in mouse models, human and mouse cell models, and post-mortem human brain tissue of different neurological diseases is essential to understand how glia are involved in cognitive decline in eg. AD and stroke.

The role of microglial cells in brain diseases

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Ten years ago we promoted the concept that microglial activation is not an all or none process but is highly diverse depending on the type of pathology and time point during the pathologic process. We have, therefore, studied aspects of microglial properties in mouse models of Alzheimer's Disease, schizophrenia, and glioma. In Alzheimer's Disease two functions of microglial cells are impaired, namely the phagocytic activity and the ability to respond to a local injury. Phagocytic activity is controlled by P2Y6 receptors and we recently found that also purinergic signaling is impaired. An impairment of phagocytic activity was also found in microglia isolated from a mouse model of schizophrenia. In glioma, microglial and invading monocytes accumulate and these glioma associated brain macrophages (GAMs) phagocytic activity is increased. The GAM phenotype is altered in a very characteristic manner not reflecting the classical M1 or M2 phenotype of activation. We found two mechanisms altered in GAMs which helped to promote glioma growth, namely the upregulation of metalloproteases MT1/MMP and MMP9. This supports the hypothesis that microglial cells can obtain diverse phenotypes depending on the pathologic state.

Microglia and meningeal macrophages in brain's health and disease

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Recent advances have directed our knowledge of the immune system from a narrative of self vs. non-self to one in which immune function is critical for homeostasis of organs throughout the body. This is also the case with respect to the central nervous system (CNS). CNS immunity exists in a segregated state, with a marked partition occurring between the brain parenchyma and meningeal spaces. While the brain parenchyma is patrolled by perivascular macrophages and microglia, the meningeal spaces are supplied with a diverse immune repertoire. Convention may imply that meningeal immunity is an ominous threat to brain function, however, recent studies have shown that its presence may instead be a steady hand directing the CNS to optimal performance. Complex organisms have co-evolved with viruses, foreign pathogens, and commensal microbial communities, allowing for the formation of immune systems capable of balancing efficient immune responses to pathogens while blunting autoimmunity. Evolutionary pressure has also established specialized organ systems capable of responding rapidly to environmental and internal changes. Emerging evidence that the immune system, independently of its antimicrobial function, plays a crucial role in organ homeostasis provides us a novel concept and lens in the attempt to analyze and understand the immune system. This applies especially to the brain, which is the master organ responsible for executive function of advanced organisms, innervation of nearly all of the body's organ systems, and speedy modulation of peripheral immune function.

Macrophages in stroke lesioned brain

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Stroke is the second most common cause of death worldwide and a major cause of disability. In ischemic stroke, different types of neurons and glia cells die within a restricted brain area over a short time period due to restricted oxygen and nutrient supply. Apart from thrombolysis and thrombectomy during the first hours after an ischemic stroke, which can be given to only a fraction of patients, no effective treatment to improve functional recovery exists in the post-ischemic phase. Following stroke, the ischemic lesion triggers inflammation, i.e., activation of resident microglia and infiltration of immune cells from the blood. The activated microglia and infiltrating monocytes become macrophages and produce pro- and anti-inflammatory mediators which could be detrimental and/or beneficial, respectively, for post-stroke functional recovery. Previously, we showed that depletion of monocyte-derived macrophages (MDM) during the first week after stroke abolished long-term behavioral recovery and drastically decreased tissue expression of anti-inflammatory genes including TGFbeta, CD163, and Ym1. Taken together, our observations raised the possibility that MDM play an important role in post-stroke recovery through activation of anti-inflammatory factors.
It has been shown that choroid plexus specifically mediates beneficial M2 macrophages infiltration after spinal cord injury. Whether choroid plexus plays similar roles after ischemic stroke remains unknown. Our recent study showed that in cortical stroke choroid plexus responds by upregulation of gene expression for several possible mediators of MDM migration and, concomitantly, MDMs increase in choroid plexus and cerebrospinal fluid (CSF). Thus, choroid plexus probably plays certain role as a route for M2 MDM infiltration after stroke. We also have shown that MDMs delivered into CSF infiltrate the ischemic hemisphere and, if they have been primed in vitro to M2 phenotype, they promote post-stroke recovery of motor and cognitive function without influencing infarct volume. These data suggest the possibility that autologous transplantation of M2 MDMs into CSF might be developed into a new strategy for promoting recovery also in patients with stroke.

Therapeutic plasticity of neural stem cells

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Recent evidence consistently challenges the sole and limited view that neural stem/precursor cells (NPCs) may protect the central nervous system (CNS) from inflammatory damage leading to neurodegeneration exclusively throughout cell replacement. As a matter of fact, NPC transplantation may also promote CNS repair via intrinsic neuroprotective bystander capacities, mainly exerted by undifferentiated stem cells releasing, at the site of tissue damage, a milieu of neuroprotective molecules whose in situ release is temporally and spatially orchestrated by environmental needs. This milieu contains molecules (e.g. immunomodulatory substances, neurotrophic growth factors and stem cell regulators), which are constitutively expressed by NPCs for maintaining tissue homeostasis either both during development and adult life.
The intrinsic nature (pleiotropism and redundancy) of these molecules as well as their 'constitutive' characteristics, may also reconcile data showing that other sources of somatic stem cells (e.g. mesenchymal stem cells), with very low capabilities of neural (trans) differentiation, may efficiently promote CNS repair.
Thus, cell plasticity can also be viewed as the capacity of somatic stem cells to adapt their fate and 'therapeutic' function(s) to specific environmental needs occurring as a result of different pathological conditions (i.e. therapeutic plasticity). The challenging ability of transplanted NPCs to protect the brain from several types of injuries using different and/or articulated bystander strategies is of pivotal importance for the future of stem cell based therapeutic approaches.

Cellular mechanism of thyroid dysfunction in the central nervous system

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Thyroid hormones (THs) are essential for the development and function of the central nervous system (CNS). In the CNS, circulating thyroxine (T4) crosses blood-brain barrier via specific transporters and is taken up to astrocytes, becomes L-tri-iodothyronine (3, 3', 5–triiodothyronine; T3), an active form of TH, by type 2 de-iodinase (D2). T3 is released to the brain parenchyma from astrocytes (glia-endocrine system). In adult CNS, both hypo- and hyper-thyroidism, the prevalence in female being >10 times higher than that in male, may affect psychological condition and potentially increase the risk of cognitive impairment and neurodegeneration including Alzheimer's disease (AD).
We have reported that non-genomic effects of T3 on microglial functions and its signaling [1] and sex- and age-dependent effects of THs on glial morphology in the mouse brains of hyperthyroidism [2, 3]. Behavioral changes also showed sex-dependence. For example, using young mice with hyperthyroidism, male mice showed increased locomotor activity, while female mice showed depressive behavior without changes in locomotor activities. Synaptic spine in hyperthyroidism was analyzed as well. Male mice showed increase spine density without any changes in spine volume, while female mice showed more significant increase in spine density with decreased spine volume. Results using aged mice or opposite thyroid dysfunction, hypothyroidism, will be also shown and discussed. These results may help to understand physiological and/or pathophysiological functions of THs in the CNS and how hypo- and hyper-thyroidism affect psychological condition and cognition.

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Astrocytosis as an Early Event in the Time Course of Interactive Pathological Processes in AD as Revealed by PET

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Alzheimer´s disease (AD), the most common neurodegenerative disorders, is characterized by a complex neuropathology involving deposition of extracellular amyloid –ß plaques , intracellular neurofibrillary tangles an activation of glia cells, astrocytes and microglia leading to cognitive dysfunctions. Several positron emission tomography (PET) radiotracers are available to image different pathophysiological processes in AD. The abundant reactive glia cells surrounding beta amyloid plaques and their role in AD remains poorly understood especially in early stage of AD disease. In absence of specific astrocyte PET biomarkers monoamine oxidase B (MAO-B) has been used a surrogate target. Recent studies using 11C-deuterium-L-deprenyl (11C-DED) PET imaging suggest that astrocytosis may be present at very early stages of disease development of AD. High 11C-DED binding has been observed in patients with mild cognitive impairment (MCI) and even more interestingly in presymtomatic autosomal dominant AD mutation carriers more than 17 years before expected clinical symptoms. While the amyloid-ß plaque load measured by PET shows a divergent trajectory and increases with AD disease severity both the 11C-DED binding and cerebral glucose metabolism (18F-FDG) decline longitudinally with as the disease progression. The decline in the functional astrocyte marker MAO-B might reflect reduced glucose demand by astrocytes due to neurodegeneration and reduced glucose utilization or lactate availability for the adjacent neurons. It is reasonable to speculate that in preclinical stages of AD amyloid –ß oligomers may cause MAO-B overexpression in astrocytes. By using structural and diffusion magnet resonance imaging (MRI) for calculation of mean diffusivity (MD) in presymptomatic ADAD carrier the 11C-DED binding was found to be negatively correlated to MD and positively correlated with cortical thickness. In addition to 11C-DED there are presently attempts to develop new astrocyte PET biomarkers and BU99008 is an interesting candidate assumed to label imidazoline receptors predominantly present in astrocytes. Development of novel, more specific, and sensitive astrocyte biomarkers will make it possible to target chemical pathways that may preserve beneficial astrocytic functions in response to AD pathology. A still quite unexplored research is the relationship between astrocytes and tau deposition in AD.

Activity-dependent plasticity of synaptic astroglial environment

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Memory formation is thought to involve structural remodelling of synaptic connections. Whether and how this engages the perisynaptic microenvironment inhabited by astroglia is poorly understood. We combine single-cell electrophysiology with two-photon excitation microscopy, photolytic uncaging, super-resolution techniques, and correlational 3D electron microscopy, to monitor fine astroglial morphology during the induction of synaptic long-term potentiation (LTP). We find that LTP induction protocols, either in multiple or in individual identified synapses, in acute slices or in vivo, trigger nanoscopic withdrawal of perisynaptic astroglial processes near potentiated synapses. The underlying cellular mechanisms do not depend on major cascades of astroglial Ca2+-dependent signalling but require the astroglial ion exchanger NCCK1 also involving the actin-controlling protein cofilin. The LTP-associated reduction in synaptic astroglial coverage boosts extra-synaptic glutamate escape thus facilitating NMDA receptor-mediated cross-talk among neighbouring synapses. Thus, LTP induction can alter the spatial profile of neurotransmitter actions and thus signal integration rules, in the extracellular proximity of potentiated synapses.

Astrocytes and stem cells in pathophysiology of ageing and neurodegenerative diseases

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Extrasynaptic (volume) transmission, mediated by the diffusion of neuroactive substances in the extracellular space (ECS), plays an important role in short- and long-distance communication between neurons, axons and glia [1]. The structure of cellular aggregates, astrocytes and the extracellular matrix (ECM) channel the migration of molecules in the ECS, so that diffusion in CNS is heterogenous, and in certain regions is facilitated in one direction rather than another. This diffusion anisotropy has been found in myelinated white matter, cerebellum and hippocampus, and may be of importance for neuron-glia communication 'spill-over' of mediators and 'cross-talk' between synapses. Changes in ECS volume and geometry determined by diffusion analysis using ion-selective microelectrodes or by diffusion-weighted NMR, accompany physiological neuronal activity, development and aging, as well as pathological states. The structural changes, particularly astrogliosis, astrocyte pathology and extracellular matrix (ECM), increase diffusion barriers which results in the loss of diffusion anisotropy, and in the damage of perineuronal nets (PNNs). These changes affect the efficacy of neuron-glia communication, synaptic and extrasynaptic transmission, and the damage of the nerve cells.

Neurodegenerative diseases (ND) such as Alzheimer's disease (AD), spinal cord injury (SCI), and amyotrophic lateral sclerosis (ALS) represent a group of diseases with human protein-misfolding and ECM disorders. Astrocytes play a key role in these pathologies as they secrete neurotrophic factors that stimulate neurogenesis, stimulate synaptogenesis and maintain optimal PNNs which are important for neuronal vulnerability and CNS plasticity [2]. Reactive astrocytes are closely associated with β-amyloid plaques (AD), gliotic scars formation (SCI) and a disfunction of perineuronal nets (ALS).

Stem cells have been investigated for their therapeutic potential in ND. Implantations of human mesenchymal stem cells (MSCs), a conditionally immortalized stem cell line from fetal spinal cord (SPC-01) and induced pluripotent stem cell-derived neural precursors (iPS-NPs), labelled in culture with iron-oxide nanoparticles for MRI tracking, were studied for their capacity to migrate towards lesion sites, differentiate, induce better regeneration, preserve PNNs and stimulate neural plasticity [3]. It was found that animals with SCI lesions improved their function, and animals with ALS had a prolonged lifespan and a decreased motoneuronal loss.

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Principles of astrogliopathology

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The common and prevailing set of neurological thoughts considers neurones as the primary substrate of pathological progression. This "neurone-centric" concept, however, undergoes a dramatic change. It has become universally acknowledged that the homeostasis of the nervous tissue is regulated by a complex fabric of neuroglial cells. Astroglia in particular represent a main element in the maintenance of homeostasis and providing defense to the brain. Consequently, dysfunction of astrocytes underlies many, if not all, neurological, neuropsychiatric and neurodegenerative disorders. General astrogliopathy is evident in diametrically opposing morpho-functional changes in astrocytes, i.e. their hypertrophy along with reactivity or atrophy with asthenia. These complex plastic changes underlie pathophysiology of all neurological disorders including genetic, (e.g. Alexander disease, which is a primary sporadic astrogliopathy), environmentally caused, (e.g. heavy metal encephalopathies or hepatic encephalopathies), neurodevelopmental (e.g. different forms of autistic spectrum disorder) or neurodegenerative (e.g. amyotrophic lateral sclerosis, Alzheimer's and Huntington's diseases).

Microglia in the aging brain

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Microglia are among the longest-lived mammalian cell types, residing in the brains of mice for years and humans for decades. During this period, microglia peruse the brain parenchyma with ramified processes to sense perturbations and respond with specialized compensatory functions. We used electron microscopy to analyze microglia in histological brain sections from old mice and rediscovered a forgotten, lipid-droplet accumulating microglia state. Lipid droplets, i.e. lipid storing organelles that contain neutral lipids such as triacylglycerols and cholesterol, are increasingly recognized as structural markers of inflammation. Peripheral immune cells form lipid droplets as a response to inflammation and stress, including macrophages in atherosclerotic lesions, leukocytes in inflammatory arthritis, and eosinophils in allergic inflammation. There, lipid droplets are involved in increased production of inflammatory cytokines and altered cellular functions. We found microglia with lipid droplets represent over 50% of microglia in the aging hippocampus and exhibit a unique transcriptional signature. They show defects in phagocytosis, produce increased levels of ROS and secrete high levels of proinflammatory cytokines. By using pooled, genetic CRISPR-Cas9 knockout screening, we discovered genes that have been previously linked to neurodegeneration (SLC33A1, VPS35, PGRN) as genetic modulators of lipid droplet formation in microglia. Remarkably, knockout of PGRN, which is involved in the development of frontotemporal dementia, resulted in severe accumulation of lipid droplets in microglia in PGRN-/- mice in vivo. Together, these findings show that the presence of lipid droplets represents a novel state of microglia with a unique transcriptional signature and functional impairments in the aging brain and suggests these cells may play a role in neurodegenerative diseases.

Noradrenergic Regulation of Astroglial Function in Health and Disease

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Impairment of the main noradrenergic nucleus of the human brain, the Locus coeruleus (LC), which has been discovered in 1784 by Félix Vicq-d'Azyr (1748–1794), a French physician and neuroanatomist, represents one of defining factors of neurodegenerative diseases progression. Projections of LC neurons release noradrenaline, which stimulates astrocytes, heterogeneous, homeostatic neuroglial cells enriched with adrenergic receptors. There is a direct correlation between the reduction of noradrenergic innervations and cognitive decline associated with ageing and neurodegenerative diseases. It is, therefore, hypothesised that the resilience of LC neurons to degeneration influences the neural reserve that in turn determines cognitive decline. Deficits in the noradrenergic innervation of the brain might be reversed or restrained by increasing the activity of existing LC neurons, transplanting noradrenergic neurons, and/or using drugs that mimic the activity of noradrenaline on astroglia. In this lecture these strategies will be discussed along with presenting how the activation of adrenergic receptors modulate the morphology (cytotoxic edema), aerobic glycolysis and vesicle-based signaling in astrocytes. In particular we will address how fingolimod and ketamine, two established drugs used to treat neuroinflammation in multiple sclerosis and major depression, respectively, affect astrocytes.

Poster Presentation Abstracts

Characteristics of feeding neuronal centers in representatives of invertebrate phyla - Annelida and Mollusca.

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Feeding disorders are a big problem for today's society. In this respect, it is very important to define evolution of feeding neuronal centers. Stomatogastric nervous system related to feeding motor activity and associated serotonergic modulatory neurons in a representative of invertebrate phylum annelida – medicinal leech, was characterized earlier (Mesce KA et al., J of Exp Biol, 2018, 221, jeb175687). Based on molecular data, annelids and mollusks share the same evolutionary clade – Lophotrochozoa. The aim of the current study was to compare feeding nervous centers of medicinal leech and representative of gastropod mollusk herbivorous pond snail Lymnaea stagnalis; The stomatogastric nervous system of the leech consists of five ganglia, three of which innervate three jaws. In gastropod mollusk Lymnaea stagnalis there are two buccal ganglia that innervate buccal musculature. At the same time, there were pronounced similarities between serotonegic modulatory neurons. Difference in number and size of stomatogastric and buccal ganglia could be related to distinctive feeding strategies, while great resemblance of serotonergic modulatory neurons of two separate phyla points to the conservation of this neuromodulatory system.

The electromagnetic stimulation effects on learning and memory in genetically epilepsy-prone rats

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Electro-magnetic field (EMF) appears to be biologically active, penetrating into the living tissue without any impediment. It is used as a complementary to the drugs, for treating different neurodegenerative diseases (Parkinson's disease, schizophrenia, depression, tinnitus, etc.) Deterioration of the cognitive function is associated with epilepsy. Antiepileptic drugs lead to memory damage. Therefore, we decided to study the effects of acoustic range electric magnetic stimulation (EMS) on learning and memory functions in genetically prone to audiogenic seizure rats (GEPRs) and inbred white rats (n=14) by the use of a multi-branch maze. For this task a part of GEPRs and a part of inbred rats were stimulated with EMS (10000 Hertz, 1,5 m/Tesla, during 5 days, 20 min per day), which changed behavioral seizure manifestations in GEPRs. EMS decreased the number of errors (getting in the deadlock branch) that the rat was making to reach the destination and the time needed for passing the maze in both groups, especially in GEPRs. The time needed to reach the destination was less in GEPRs ($p \leq 0.05$) compared to inbred ones. We assumed that EMS decreases anxiety and enhances exploratory activity of the GEPRs. EMS in GEPRs improve their memory

and this may lead to a new treatment for memory improvement. The positive effects of EMS on learning and memory functions has been detected. Therefore, acoustic range EMS can apply for partial or complete suppression of seizures and improvement of memory function. These results provide further insights for a better understanding of the fundamental neurobiology of memory.

The role of orexin-A on electrophysiological changes induced by the kainic acid model of temporal lobe epilepsy

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Neuropeptide orexin/hypocretin was found to be linked to coordination/regulation of various physiological processes. The complexity of its action is primarily created by the wide range of orexin (OX) neuron projections. The distribution of OX receptors in the hippocampus, suggests a possible importance of OX in the control of the hippocampal related functions. Both pro-convulsive and anti-epileptic efficiencies of OX have been found using different experimental approaches and epilepsy models. These discrepancies in the literature prompted the necessity for additional investigations, as the orexinergic system appears to be a hopeful target to treat the epilepsy-related dysfunctions. In vivo electrophysiological experiments were performed to investigate the effects of intracerebroventricular application of OX (A and B, 10µl) on background spiking activity and evoked field responses of the hippocampus. Bipolar intrahippocampal single and paired electrical stimulation of CA1/CA3 fields were performed in wild type and kainic acid-status epilepsy (KA-SE) rats. Our experiment showed that OX-A decreases amplitude and increases the frequency of baseline activity in CA1, no significant changes were observed in CA3. Changes in CA1 were accompanied by concomitant reduction of duration of the responses. The amplitude of single evoked responses was increased in CA1 after OX-A injection. OX-B was ineffective, indicating involvement of OX1 receptors in the effects of OX-A. OX-A has no effect on paired pulse facilitation in CA1 showing its postsynaptic action. Alterations caused by kainate-model of epilepsy were different in CA1/CA3 fields and KA-SE shifts the character of influence of OX-A in these fields. The possible mechanisms are discussed.

Astrocyte-based neuroprotection for traumatic brain injury

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Excitotoxicity is considered as main factor in the pathophysiology of traumatic brain injury (TBI). Antagonists of excitatory amino acids (EAAs) fail to become the main strategy against TBI because of narrow therapeutic window and undesirable side-effects. Therefore, it is necessary to develop alternative strategies against TBI. Lithic

acid (LA) was previously supposed as neuroprotective that could be mediated by the increasing EAA transporters on astrocyte membranes. Since astroglial EAAs mediate excitotoxicity processes, we hypothesized that LA can persist it. For observation of LA neuropharmacological efficacy, well-characterized equibiaxial stretch injury model of hippocampal organotypic cultures was utilized. Cell death was evaluated by propodium iodide fluorescence (PI) microscopy; Input-output currents (IOC) and paired pulse ratio (PPR) recorded from all surface of the hippocampus served to assess functional properties of treated vs untreated tissues to find optimal for drug dozing and therapeutic window. PI method revealed less cell death in cultures treated with 30μM UA when used up to 30min post-injury. Parameters from IOC and PPR measurements (Rmax, I50, PPR) did not simply accord morphological data, but interestingly, injured-cured cultures showed opposite to uninjured tissues direction of changes in electrophysiological parameters and vise versa. Our research revealed neuroprotective effect of astrocyte-based approach after TBI as well as showed that it involves in synaptic plasticity processes. We suggest that these specific physiological alterations can be important tool for neural tissue to activate mechanisms, which help it to survive after TBI in condition of excitotoxicity.

Role of Schwann cell in preventing Thrombin from Damaging Nerves

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Thrombin, a molecule associated with blood clotting has been found to play an important role in nerve degeneration. Schwann cells have been found to create protective insulation around the axons and help form synapses and protect nerves by blocking thrombin as well as other potentially destructive enzymes released by muscle cells. This was confirmed when In a mouse model with absence of Schwann cells, the NMJ synapse degenerated after two days. Without Schwann cells, acetylcholine–the signaling molecule in NMJ–was found to be a major culprit in why the nerves degraded because it prompted muscle cells to release thrombin that degraded the nerve. A mouse model where thrombin was absent, found that these mice experienced less nerve axon degeneration affirming the role of thrombin in nerve axon degeneration. In a mouse model with a mutated erbB3 — a gene required for Schwann cell development — it was found that NMJ synapses and motor neurons degenerated within a short time. Absence of Schwann cells can lead to the degeneration of neurons, which, in turn, is related to conditions such as MS, ALS, Alzheimer's disease, and schizophrenia and this study can be helpful for these diseases, where thrombin accumulation or dysregulation and neuronal degeneration has been implicated. Drugs like Tacrolimus (FK 506) can enhance proliferation of Schwann cells thereby provide protection to nerves from thrombin and other enzymes in neurodegenerative diseases.

Functions of astroglial domains and the importance in pathologic processes

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Purpose: Review the research about structural function of astrocytes and determine possible importance of astroglial domains in epileptic brain. Astroglial domain is three-dimensional anatomical territory created by each astrocyte. Recent research has focused on possible physiological functions of astroglial domains and the importance in pathologic processes. In particular, disruption of the normal astroglial domain pattern has been linked to post-traumatic epilepsy. Normally Domains are regularly spaced and parcel gray matter into relatively independent units. The overlap between territories of neighboring astroglial domains is minimal and it does not exceed five percent. Study, using diolistic labeling showed 10-fold increase in the overlap of processes in epileptic mice brain. Valproate, common antiepileptic, reduced the overlay of astrocytic processes. Conclusion: Reorganization of astrocytes may form the structural basis for recurrent excitation in the epileptic brain, in concert with dendritic sprouting and new synapse formation.

Stress Induced Glial Cells Activation: An Integrative Approach to Neuroinflammation Involved in Neuropsychiatric Disorders

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Increasing evidence of knowledge indicates that adolescence stress is associated with an increased risk of developing neuropsychiatric disorders in adulthood. Adolescence is a critical and sensitive period of brain development that characterized by changes in brain structure and function, particularly in limbic and cortical regions (hippocampus, amygdala and prefrontal cortex). Several lines of evidence revealed that glial cells such as microglia, astrocytes and oligodendrocytes substantially impact on neuronal function and activities and are significantly involved in the underlying pathobiology of neuropsychiatric disorders. Glial cells activation leads to an ongoing pathologic process in the central nervous system includes neuroinflammation, cellular destruction, glial cell dysfunction and stimulation of the hypothalamic-pituitary complex. Chronic stress activates microglia in the medial prefrontal cortex, triggering inflammation related cytokines, leads to impaired neural responses in the mPFC, resulting in depressive behavior. The prefrontal cortex (PFC) as a last cortical region has been implicated in many psychological disorders and is involved in cognitive processes that are influenced by oxidative stress and inflammation. Inflammatory cytokines and immunomodulatory molecules released by glial cell during stress may promote many of the behavioral effects of acute and chronic stress; resulting stress impaired cognitive functions and

induced neuropsychiatric disorders. It seems glial cell degradation are postulated to be critical factors contributing to the aggravation of depressive-like symptoms. It can be concluded that stress may be an important factor in the degenerative processes in the development of neuropsychiatric disorders. Therefore, new strategies to reduce the deleterious effects of stress should be explored for the prevention and treatment of brain disorders.

Multiple origins of reactive astrocytes after closed-head injury

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Reactive astrocytes are a hallmark of brain injury, but their diversity and implication in tissue degeneration and recovery are largely still to be elucidated. Focal brain injury created by illuminating mouse cerebral cortex with intense light through thinned-skull cranial window induced distinct reactive astrocyte subpopulations, which were labelled specifically by using Nestin-, GFAP- and GLAST-CreERT2. Nestin-CreERT2 labeled NG2 glia within lesion core and some of these cells gradually increased astrocyte markers in two weeks. The reactive astrocytes derived from NG2 glia expressed extracellular matrix proteins and formed the border between lesion and perilesional region. Nestin-CreERT2 also labelled neural stem cells in subventricular zone and some of these cells migrated to perilesional lesion to become reactive astrocytes. The reactive astrocytes derived from neural stem cells as well as those labelled by GFAP-CreERT2 bore nestin positive long projecting fibers covering perilesional cortical recovery. These nestin-positive reactive astrocytes alone showed calcium response to glutamate, and the elimination of these cells impaired tissue recovery. GLAST-CreERT2 labelled astrocytes even before injury and these astrocytes became perilesional nestin-positive as well as distal nestin-negative and hypertrophic reactive astrocytes. These results indicate multiple origins of reactive astrocytes, which are potential therapeutic target for specific modulation of cerebral degeneration and recovery.

Features of glial cells in vitro

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Our studies of the spinal cord of 14-day-old chicken embryos and the cerebral cortex of newborn rats in vitro showed that glial cells play an important role in the regulation of viable neurons. In intact cultures, active migration of glial cells in the explant growth zone is observed, forming a substrate for axon growth. Glial cells also promote axon growth when plasma or fibrous astrocytes, attaching to the end of the axons of nerve cells or to their collaterals, facilitate their movement over a considerable distance. In a dissociated culture of the spinal cord of chicken embryos, glial cells form oriented radial rows along which neurons are localized. This process is similar to the migration of neuroblasts during histogenesis from the ventricles of the brain into various

structures of the brain along the processes of radial glia. Active growth of glial cells was detected after stimulation with Dalargin (an analog of leu-encephalin), sometimes cells with a wave-like membrane were observed. In experiments with model hypoxia, various stages of glial body edema and large cytoplasmic vacuoles were revealed. A study of the effect of ethanol and toluene on glial cells in vitro indicates that their introduction into the culture medium inhibited the development of the growth zone, significantly reducing the number of glial cells deported from explants. The addition of antioxidants to the medium together with ethanol (Plaferon, Dolivin, Zinc sulfate) and toluene (Mirradol) prevented the damaging effect of this toxins and stimulated migration of glial cells in the explant growth zone.

Complement C3a modulates peri-infarct reactive gliosis after ischemic stroke

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Brain ischemia is a powerful inducer of reactive gliosis that serves to demarcate the lesion and restore tissue homeostasis. Prolonged reactive gliosis, can, however, inhibit ischemia-induced plasticity and recovery. Complement has emerged as a regulator of multiple neural processes including developmental neuronal migration, synaptic pruning and neuroprotection. We previously showed that signaling through the receptor for complement peptide C3a (C3aR) stimulates neural plasticity and intranasal treatment with C3a facilitates recovery after ischemic stroke (Stokowska et al., Brain, 2017). In an in vitro ischemia model, C3a increased the survival of astrocytes and reduced their expression of GFAP (Shinjyo et al, Mol Neurobiol, 2016). Here we investigated the role of C3a-C3aR axis in the regulation of post-stroke glial responses. We observed that overexpression of C3a in reactive astrocytes reduced GFAP immunoreactivity in the peri-infarct cortex 3 weeks after ischemic stroke; C3aR deficiency had the opposite effect. C3a overexpression increased whereas C3aR deficiency reduced the density of Iba-1 positive cells. Daily intranasal treatment of wild-type mice with C3a for 2-3 weeks starting 7 days after stroke induction reduced peri-infarct GFAP expression but did not affect the density of Iba-1 positive cells assessed 3 and 8 weeks after stroke. These results show that the C3a-C3aR axis regulates peri-infarct reactive gliosis exerting opposite effects on astrocytes and microglia / macrophages. Modulation of peri-infarct reactive astrogliosis may contribute to the positive effect of intranasal treatment with C3a on neural plasticity and functional recovery.

The effect of chronic toluene inhalation on short-term memory and the ultrastructure of the rat hippocampus

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Toluene is a more widely used inhalant with euphorigenic effect. One of the questions, which needs further elucidation is the fine alterations provoked by toluene chronic exposure on the brain. In the present study we investigate short and long term effect of toluene inhalation on spatial short-term memory and the ultrastructure of the hippocampus. Special accent was made on glial cells and neuron-glia interactions. For toluene inhalation in the chamber and was exposed to toluene vapor, during 40 days. Behavioral tests: Four-arm plus shaped maze was used. (i)- total arm entries, (ii)– alternation behavior (%) Electron microscopy: The ultrastructure of neurons, glial cells, and synapses of CA1 area on ultrathin sections was described using TEM JEM 14000. Results: Short-term memory was significantly affected only by 40 d toluene inhalation. Specifically, the impairment of memory was shown. Fine alterations were observed also only after 40 d of toluene exposure. Thus, moderate(mainly) destructions of mitochondria and endoplasmic reticulum(mainly) in some pyramidal cells and interneurons as presynaptic terminals with rare synaptic vesicles were revealed. Rarely irreversible pathologies - degeneration of pyramidal neurons and presynaptic terminals were seen. Glial cells were the most altered. Particularly, proliferated astrocyte processes and activated microglia were relatively common. In addition, reaction of astroglia was prominent around the degenerated neurons and some dendrites with single dendrotubules. The data indicate that toluene chronic exposure affects spatial memory. Such impairment is reflected on ultrastructural level of the hippocampus. The data also confirm that the role of the hippocampus in spatial memory.

Characterization of predictive power of extracellular signal recordings in a global ischemia animal model

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Introduction: Vascular dementia, the second most prevalent type of dementia after Alzheimer's, is a clinical sign of chronic cerebral hypoperfusion. Early detection of ischemic injury and prevention of neuronal death are one of the current global biomedical issues. We suppose that local field potential (LFP) recording can be a sensitive tool in detecting ischemic damage of the tissue in both early and late stages of cerebral hypoperfusion and in monitoring neural activity changes during the progressive hypoperfusion in vulnerable areas.
Objectives: The aim of the research was to provide characteristic LFP alterations recorded during an acute phase of the global cerebral ischemia and their predictive power.
Methods: The unilateral carotid artery occlusion (UCCAO) is a widely-practiced model of chronic ischemic brain damage, which in the first days also allows us to explore acute ischemia-induced neuronal changes like after stroke. The electrical activity of the brain was registered with a custom-made neural probe. The signal was amplified, filtered, digitized and acquired with Intan amplifier and USB interface boards. The recordings were obtained from parietal cortex of the rats both in normal

condition and on the following day after implementing UCCAO model. The data analysis and classification were performed using NI DIAdem software and custom-written code in IPython environment.
Results: In Fourier spectrograms of intact brain recordings, a peak at 14.4-15 Hz frequencies was detected, whereas this phenomenon was absent in global ischemia model recordings. In channels' cross-correlograms for intact brain and global ischemia recordings, there was a clear difference of the maximum peak power. With autocorrelation analysis, the long lag rhythmicity was detected in normal brain recordings, while no rhythmicity in ischemic brain recordings was seen.
Conclusion: We have analyzed and described the major characteristics of the neural population electrical activity that vary between normal and global ischemic brains. This data proves that LFP can be used for further investigation in normal, acute, and chronic ischemic brains. We are planning to improve the current method in the future using more samples, to record the same samples after a longer time of ischemic injury, and to get stronger evidence for the signatures we identified.

Myelin basic protein charge isomers and glutamate affect macrophage polarization

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During a neuronal injury, a variety of immune cells infiltrate into the local microenvironment at the demyelination site. Macrophages are a functionally heterogeneous cell population and depending on microenvironments they polarize in two main groups: M1 and M2. After the destruction of the intact myelin sheath, its major constituent myelin basic protein (MBP) dissociates from the plasma membrane and acts as a free ligand on the infiltrated immune cells. We showed that different charge isomers of the MBP (C8 - that is least positively charged and most modified isomer and C1 - that is least modified and most positively charged isomer) induce different effect on macrophages: deiminated C8 isomer tends to polarize RAW264.7 macrophages into M1 phenotypes, whereas C1 enhances the activity of M2 phenotype markers. Except for the mechanisms described above, we also tried to study the influences of glutamate - and its receptor - mGluR5 (as components of inflammatory microenvironment) on macrophage polarization. We showed that extracellular glutamate and mGluR5 could be involved in macrophage plasticity by increasing the expression of transcription factor PPAR-γ and EAAT2 transporter. From the same experiments, we can deduce that regulation by glutamate shifts macrophage polarization to the M2 isoform. The results from these works can be used as a tool of an inflammation management strategy in the treatment of neurodegenerative disorders.

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Timed social multitasking: piloting a new paradigm

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The aim of the present study was to develop a new paradigm to investigate timed social multitasking. Thirty younger neurotypical healthy adults with ages ranging between 18 and 32 years participated. Participants performed a timed task-switching procedure, in which they have to shift attention between social and neutral mental sets. For the social judgment, participants have to associate labels for themselves (you) and unfamiliar people (stranger) with geometric shapes; for the neutral judgment, participants have to identify the type of geometric shape (square and triangle). Two different preparatory intervals (500 ms and 1,500 ms) predicted the upcoming task type (i.e., social judgment vs. neutral judgment task) in the current trial with 90% probability. We found that participants responded faster in trials with expected combinations of preparatory interval and task type compared to trials with unexpected combinations of preparatory interval and task type. This means that participants learned the associations between interval and task type. Our results suggest that participants were able to form time-based expectancies for task type in the social task-switching paradigm.

Early postnatal noise exposure affects development of perineuronal nets in the rat central auditory system

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In the rat auditory system, a period of increased vulnerability to external stimuli (known as the critical period, CP) starts with the onset of hearing at postnatal day 12 (PD 12) and ends around three weeks later. It is expected that the closing of the critical period is paralleled with the maturation of perineuronal nets (PNNs), lattice-like extracellular matrix structures that appear around the soma and proximal dendrites of mainly parvalbumin expressing inhibitory neurons. The exposure to loud sound during the CP, can significantly affect neuronal structure (Ouda et al. 2014) and function of neurons in the rat auditory system (Grécová et al. 2009). Whether the exposure can also change the pattern of PNN maturation remains unknown. Long-Evans rats were exposed at PD14 to a 125 dB SPL broad-

band noise for 8 min. The content of PNNs was evaluated in brain sections, stained for Wisteria floribunda agglutinin in exposed rats aging from PD14 to PD106, and compared with non-exposed controls. PNN appeared at PD21 in both groups, however, in a significantly greater number in exposed than control animals. The number of PNNs further increased at PD28, but the difference between groups remained. The development of PNNs of both groups had aligned since PD35. The early development of PNNs therefore appeared to be more accelerated in the noise-exposed animals than the non-exposed controls. These results suggest that noise exposure may lead to a premature closing of the CP window, thus limiting the plasticity of early postnatal development in the auditory cortex.

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The Pathway of Neuroglial Activation During Alzheimer's Disease

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Alzheimer's is the most common disease in 21st century. It can appear at any age, especially in older people and usually develops gradually as a problem of thinking, memory and behavior. Nowadays AD is an incurable and terminal disease. A number of hypotheses have been advanced to explain AD, for example: tau phosphorylation, amyloid-beta (Aβ) plaques, organophosphate poisoning and etc. As we know there are a lot of risk factors, that cause AD. Glial cells are becoming the focus of recent researches pertaining the pathogenesis of neurodegenerative disorders, Alzheimer's Disease (AD) in particular. In fact, activated microglia is the main determinant of neuroinflammation, contributing to neurodegeneration. The main molecular bases of AD, namely OS, neuroinflammation and dysfunctional GSK-3 pathway share neuroglia as a co-determinant and/or target. Recent evidences suggest a reliable role of neuroglia and OS-induced neuroglial alterations in AD. DNA damage indicates the presence of compromised astrocytes that could not be able to effectively support neurons as usual. Aβ and NFTs contribute to the oxidative damage to oligodendrocytes, further altering the myelination process. To conclude the glial changes occurring from the early to the advanced disease stages could considerably contribute to the neurodegenerative process. However, the role of neuroglia in neurodegeneration is still broadly debated. Further studies are needed to shed light on such a complex as well as fascinating topic.