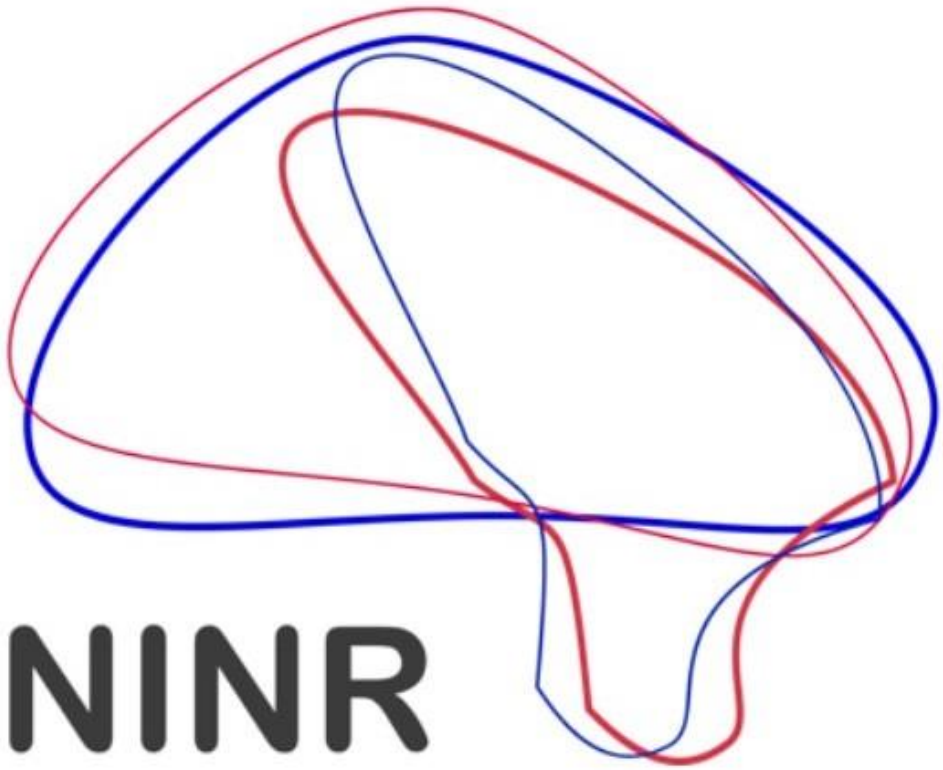
NATIONAL INSTITUTE FOR NEUROLOGY RESEARCH
CZECH REPUBLIC



SCIENTIFIC REPORT
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CZECH RECOVERY PLAN

MINISTRY OF EDUCATION, YOUTH AND SPORTS

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NATIONAL INSTITUTE FOR NEUROLOGY RESEARCH – CZECH REPUBLIC

Research and treatment of neurological disorders is a rapidly changing field of medicine. Advances in molecular genetics and disruptive technological innovations are transforming medical research and health. They open the prospects for introducing innovative diagnostic and therapeutic approaches that can change the trajectory and prognosis of brain disorders that are currently impossible to cure. The mechanisms of many neurological disorders including neurodegenerative and neurodevelopmental diseases remain enigmatic. Here, the traditional reductionist approach of the 20th century has failed to bring seminal breakthroughs and curative treatment.

Driving by WHO Intersectoral Global Action Plan on Epilepsy and Other Neurological Disorders 2022–2031 that was approved at the 75th World Health Assembly in May 2022 and with a generous support of EU (Next Generation EU program) and Ministry of Education, Youth and Sports of the Czech Republic (namely EXCELES program VES1/2021 from the National Recovery Plan) **The National Institute for Neurology Research (NINR)** was established on July 1st, 2022. Here the best neurology-focused research teams (N=48) from eleven prestigious research institutions across the Czech Republic joined to reverse the fragmentation of neuroscience research in the CR, to foster interdisciplinary brain research, and to become a new national authority which will address the brain health, social, economic and research priorities of the Czech Rep., the European Union, and worldwide. The ambition of NINR is to determine and foster national policy and strategy for the future of excellent neurological research and to create, educate and support a new generation of scientists and clinicians. These future experts will be able to perform and lead 21st century neurological research and will be equipped with tools and skills that will foster interdisciplinarity research.

For its first (kick-off) scientific action, the NINR is targeting one of the most severe neurological disorders - neurodegenerative diseases. Specifically, now we focus on three major aspects of neurodegenerative diseases - movement disorders, dementia and the hyperlink between neurodegeneration and neurodevelopmental disorders.

PARTICIPATING INSTITUTIONS

ST. ANNE'S UNIVERSITY HOSPITAL BRNO (FNUSA)
Clinical Neurology, Neuroimaging, Neurosciences
Behavioral Sciences, Radiology/Nuclear Medicine/Medical Imaging

INSTITUTE OF PHYSIOLOGY CAS (FGU)
Clinical Neurology, Neurosciences
Biochemistry/Molecular Biology, Cell Biology, Psychiatry

UNIVERSITY OF OSTRAVA (OU)
Clinical Neurology, Neuroimaging, Neurosciences
Surgery, Peripheral Vascular Disease, Psychiatry, Radiology/Nuclear Medicine/Medical Imaging

CHARLES UNIVERSITY (UK)
Clinical Neurology, Neuroimaging, Neurosciences
Psychology, Psychology Clinical

INSTITUTE OF EXPERIMENTAL MEDICINE CAS (UEM)
Clinical Neurology, Neurosciences
Biochemistry/Molecular Biology, Chemistry

BRNO UNIVERSITY OF TECHNOLOGY (VUT)
Clinical Neurology, Engineering Electrical Electronic, Computer Science Artificial Intelligence
Neurosciences, Chemistry, Engineering, Materials Science, Physics Applied, Telecommunications

MASARYK UNIVERSITY (MU)
Clinical Neurology, Neuroimaging, Neurosciences
Computer Science/Artificial Intelligence, Chemistry, Engineering, Materials Science, Physics Applied, Psychiatry

INSTITUTE OF BIOTECHNOLOGY CAS (BTU)
Neurosciences
Biochemistry/Molecular Biology, Biophysics, Cell Biology, Biology

CZECH TECHNICAL UNIVERSITY IN PRAGUE (ČVUT)
Clinical Neurology, Neuroimaging, Neurosciences
Materials Science, Physics Applied, Physics Condensed Matter, Microscopy, Audiology/Speech Language Pathology, Engineering Biomedical

PALACKÝ UNIVERSITY OLOMOUC (UPOL)
Clinical Neurology, Neuroimaging, Neurosciences
Chemistry Medicinal, Biochemistry/Molecular Biology, Chemistry, Chemistry Organic, Pharmacology/Pharmacy

INSTITUTE OF SCIENTIFIC INSTRUMENTS CAS (UPT)
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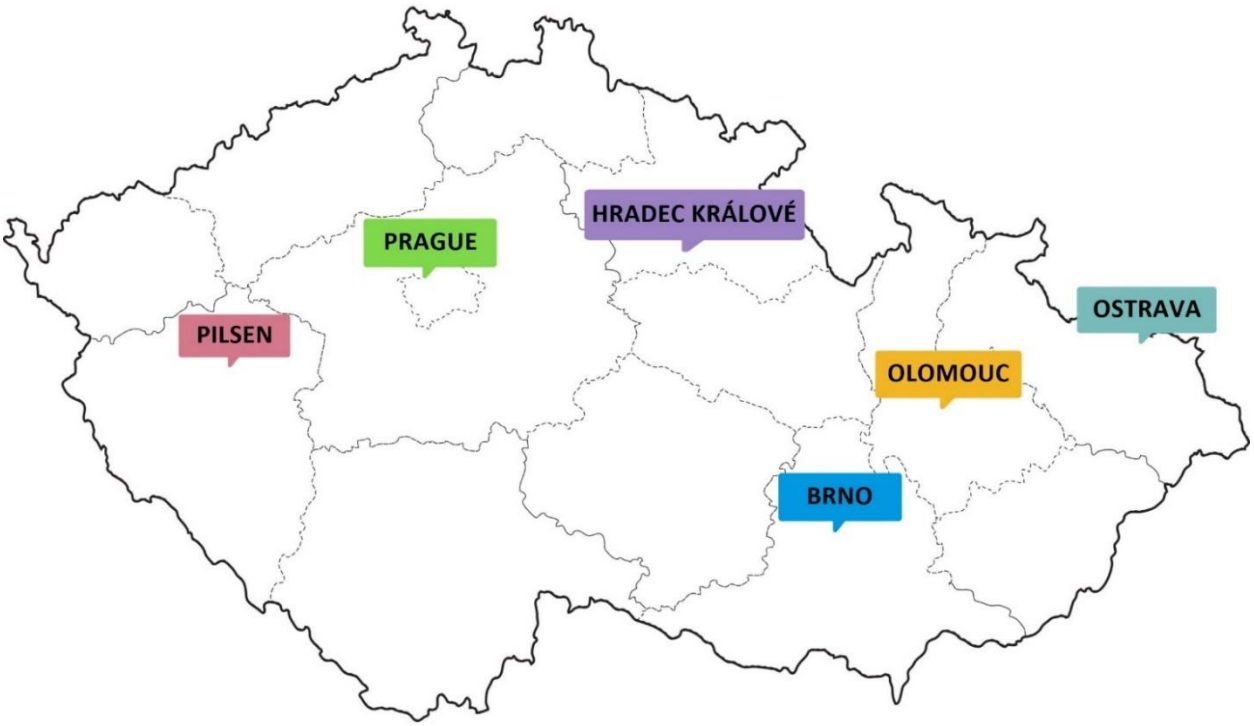
Biochemistry/Molecular Biology, Engineering Biomedical



RESEARCH WORK PACKAGES

- **Pillar 1 – Research into neurodegeneration in movement disorders**

Work package/ key objective	Key milestones – sub-objectives (leader)
WP1.1/ define early prodromal markers of neurodegenerative synucleinopathies and approaches for their population screening *Lead: doc. Dušek*	1. Establish a network of expert centers to harmonize research protocols and prepare for population screening of prodromal neurodegeneration in Czechia *(doc. Dušek)*
	2. Develop an algorithm for diagnosis and prediction of early phenoconversion in prodromal synucleinopathies based on multi-modal brain imaging *(prof. Školoudík)*
	3. Identify new biomarkers based on imaging of glymphatic system for predicting Parkinson disease progression *(prof. Rektor)*
	4. Estimate the risk of neurodegeneration as a long-term COVID-19 complication *(doc. Dušek)*
	5. Develop a methodology for recruitment of patients with prodromal neurodegeneration using social media marketing tools and deep phenotyping *(prof. Růžička)*
WP1.2/ develop new individualized approaches to DBS programming *Lead: prof. Jech*	1. Develop an individualized, multimodal, connectome-driven approach to DBS programming *(Dr. Filip)*
	2. Develop individualized, multimodal Local Field Potential power-driven approach to DBS programming *(doc. Bočková)*
	3. Evaluate non-standard DBS parameters to address non-motor symptoms in Parkinson's disease *(prof. Jech)*
	4. Find patient-based and DBS setting-based markers associated with better outcomes *(prof. Jech)*
WP1.3/ facilitate systematic genetic analyses in rare hereditary movement disorders *Lead prof. Jech*	1. Perform genotype-phenotype correlation study in a large cohort of patients with dystonia including defining criteria for advanced therapy *(prof. Jech)*
	2. Describe rare genetic causes of hereditary dystonias including their molecular underpinnings *(prof. Jech)*
	3. Describe rare genetic causes of ataxias, including the description of novel mutations *(doc. Vyhnálek)*
	4. Describe the cognitive, functional, and biochemical changes in Spinocerebellar and Friedreich's ataxias *(doc. Vyhnálek)*
	5. Establish a core facility team to study the genetic basis of movement disorders using complex structural and functional genomic methodologies *(Dr. Sikora)*

WP1.4/ describe evolution and implications of neurodegeneration in multiple sclerosis *Lead: doc. Uher*	1. Determine correlates of neurodegeneration and its predictive value for future MS disease activity *(doc. Uher)*
	2. Investigate the association between lipid profile/antioxidants and MS disease activity *(doc. Uher)*
	3. Establish joint biobanking program for MS patients and neurodegenerative disorders to translate biomarker knowledge from MS to the neurodegeneration field and vice versa *(doc. Uher)*
WP1.5/ develop objective instrumental biomarkers, telemedicine framework, and telerehabilitation assistive devices *Lead: prof. Růžička*	1. Introduce methods of kinesiological and neurophysiological analysis for remote examination and continuous monitoring of overall physical activity *(Mgr. Krupička)*
	2. Develop technologies for remote targeted training of motor and cognitive functions *(prof. Růžička)*
	3. Integrate speech assessment into clinical practice as a viable biomarker of neurodegeneration and monitoring progression in movement disorders *(doc. Rusz)*
	4. Evaluate the feasibility of remote speech screening including linguistic markers to detect motor speech and cognitive deterioration in neurodegenerative disorders *(doc. Rusz)*
	5. Evaluate neuromodulatory effects of music on brain activity and potential clinical application of music therapy in movement disorders *(prof. Rektor)*
WP1.6/ establish central brain bank and develop a methodology for detection of abnormal properties of neurodegenerative proteins in various tissues *Lead: prof. Matěj*	1. Proceeding of diagnostic algorithms, ethical issues, patient/next of kin's informed consents, and protocols of brain donation and storing *(doc. Rusina)*
	2. Establish a brain bank donation program for patients in longitudinally followed cohorts of neurodegenerative disorders *(doc. Rusina)*
	3. Perform complex molecular and neurogenetic analyses of tissue samples to study correlations of clinical, neuroimaging, biomarker, genetic, and neuropathological aspects of neurodegenerative disorders *(prof. Matěj)*
	4. Develop, optimize, and validate RT-QuIC method for detection of abnormal aggregation properties of various proteins *(doc. Holada)*
	5. Establish a structural proteomics approach to identify pathological protein folds in RT-QuIC product as a specific diagnostic and prognostic marker in neurodegeneration *(Dr. Novák)*
WP1.7/ develop potentially neuroprotective substances through advanced nano-medicinal chemistry *Lead: prof. Martásek*	1. Define, design, and prepare chelators of biologically important metal ions (*prof. Martásek*)
	2. Define, design, and prepare combined molecular structures using polyphenols *(prof. Martásek)*
	3. Define, design, and prepare nano / micro formulations, including their validation *(doc. Jakubek)*

- **Pillar 2 – Research into neurodegeneration in disorders with cognitive impairment**

Work package/ key objective	Key milestones – sub-objectives (leader)
WP2.1. Markers, risk factors and modifiers of neurodegeneration with cognitive impairment *Lead: prof. Rektorová*	WP2.1/1 Create a complex biomarkers signature of prodromal dementia with Lewy bodies subtypes *(prof. Rektorová)*
	WP2.1/2 Describe modifiable cardiovascular risk factors of cognitive decline in KardioVize population-based cohort 60+ and identify subjects at risk of degenerative dementia *(Dr. Prosecký, Dr. Gonzáles-Rivas, prof. Rektorová)*
	WP2.1/3 Characterize internal exposure agents and metabolites in patients with neurodegenerative disorders with cognitive impairment and identify prognostic biomarkers and exposure agent risk factors *(Dr. Price)*
	WP2.1/4 Use proteomics approach to identify novel biomarkers in neurodegenerative diseases: analysis of proximal fluids: tears *(Dr. Džubák)*
	WP2.1/5 Design speech/voice and handwriting/drawing-based biomarkers supporting the diagnosis of prodromal dementia with Lewy bodies *(Dr. Mekyska*)
	WP2.1/6 Define immune signature of prodromal dementia with Lewy bodies *(Dr. Frič)*
	WP2.1/7 Investigate hematoencephalic barrier dysfunction in early phases of neurodegenerative disease *(prof. Hort, Dr. Lerch, Dr.Nedělská)*
	WP2.1/8 Describe sex differences in brain structure and biomarkers in Alzheimer's disease *(prof. Hort, Dr. Nováková)*
	WP2.1/9 Assess the role of metabolic PET biomarkers for early and precision diagnostics of AD *(Dr. Čerman, prof. Hort)*
	WP2.1/10 Define blood and CSF biomarkers in neurodegeneration *(prof. Hort, Dr. Angeluci)*
	WP2.1/11 Develop and cross-validate translational diagnostic tests aimed at spatial memory *(prof. Hort, prof. Stuchlik, Dr. Laczó)*
	WP2.1/12 Establish a battery of spatial navigation tests for early and differential diagnosis of Alzheimer's disease *(prof. Hort, Dr. Laczó, prof. Stuchlík)*
	WP2.1/13 Define early neuropsychological markers of physiological and pathological aging *(doc. Vyhnálek)*

	WP2.1/14 Develop and validate a comprehensive neuropsychological battery for diagnosis of cognitive impairment in Parkinson's disease *(doc. Bezdíček)*
	WP2.1/15 Investigate age-related structural changes in neurons of the hippocampus and central auditory system in animal models of dementia *(Dr. Svoboda, prof. Syka)*
	WP2.1/16 Assess impact of lifestyle, social and spiritual wellbeing on brain health using multimodality imaging *(Dr. Nedělská, Dr.Sheardová)*
WP2.2 Impact of COVID-19 on brain function: Central mechanisms of the post-COVID syndrome *Lead: prof. Horáček*	2.2/1 Describe impact of COVID-19 on neural plasticity and brain function *(Dr. Bartečků)*
	2.2/2 Assess the function of glymphatic brain clearance system and subcellular markers of cellular injury in post-COVID syndrome *(prof. Horáček, Dr. Španiel)*
	2.2/3 Describe changes in immune phenotype in the COVID19 patients with the post-COVID syndrome *(Dr. Frič)*
	2.2/4 Use biomarkers signatures to identify subjects with a potential risk of synucleinopathies with or without cognitive impairment *(Dr. Mekyska, prof. Rektorová)*
WP2.3 Neuromodulation in the treatment of cognitive impairment in neurodegeneration *Lead: doc. Glowacki, prof. Rektorová*	WP2.3/1 Develop hardware and protocols to perform Temporal Interference Stimulation (TIS) in both animal models and humans *(doc. Glowacki)*
	WP2.3/2 Conduct an RCT targeting the cortico-hippocampal circuits by TIS *(prof. Rektorová, Dr. Nováková)*
	WP2.3/3 Evaluate the effects of low-frequency DBS of ventromedial STN for cognitive symptoms of PD *(Dr. Bezdíček)*
	WP2.3/4 Describe mechanisms of memory impairments under neural oscillations disturbances in the hippocampal system using invasive stimulation in an animal modeů *(Dr. Ježek)*
WP2.4 Basic Research leading to novel therapies *Lead: prof. Damborský*	WP2.4/1 Unravel biological function of APOE proteins and test their potential correction by small molecules *(prof. Damborský)*
	WP2.4/2 Study the interaction of neuroactive steroids with muscarinic receptors to enhance cholinergic signalling *(Dr. Jakubík)*
	WP2.4/3 Identify specific pharmacological modulators of tau spreading for Alzheimer's disease preclinical studies *(Dr. Das)*
	WP2.4/4 Use stem cells for disease modelling: Developing a pipeline for functional experiments and therapeutic targets discovery *(Dr. Bohačiaková)*

	WP2.4/5 Validate cGMP production of Mesenchymal Stem Cells for neurodegenerative diseases *(doc. Koutná)*
	WP2.4/6 Study chronobiology of Alzheimer's disease in an animal model *(Dr. Bendová, prof. Horáček)*
WP2.5 Pharmacotherapy – Clinical *Lead: prof. Hort*	WP2.5/1 Assess cognitive and survival effects of the major cardiovascular, antidiabetic and psychotropic medications among patients with different cognitive disorders *(prof. Hort, Dr. Sečník)*
	WP2.5/2 Estimate clinical, economic and caregiver effects of timely diagnosis and treatment of AD in the Czech *Republic (prof. Hort, Dr. Hlávka)*
WP2.6 Microbiome in neurodegenerative diseases with cognitive impairment *Lead: dr. Krajčovičová*	WP2.6/1 Validate the use of iPSC derived intestinal organoids as a tool to study gut-brain axis and molecular mechanisms of host-pathogen and microbiome interaction in intestinal tissue *(Dr. Frič)*
	WP2.6/2 Define role of the gut microbiome in the pathophysiology of dementia – translational research *(Dr. Khairnar)*
	WP2.6/3 Define relationships between microbiome composition and disease biomarkers and clinical outcomes. *(Dr. Price, Dr. Krajčovičová)*

- **Pillar 3 – Research into disease mechanisms common for neurodegenerative and neurodevelopmental disorders**

Work package/key objective	Key milestones – subobjectives (leader)
WP3.1/Identification of the impact of intracellular signaling alterations common for NDDs and neurodegenerative disorders on the neuronal function and dynamics of neuronal networks *Lead: dr. Novák*	1. Elucidation of the functional impact of disrupted intracellular signaling in mTOR or related cascades at the subcellular, cellular, and network levels in the genetic NDD model (*Dr. Rehorová)*
	2. Characterization of the role of the altered non-synaptic interactions between cells, homeostasis, and inflammatory state in NDD (*Dr. Novák)*
	3. Precise characterization of altered synaptic transmission emerging from neurons carrying the mutation and surrounding neurons in the NDD model *(Dr. Horák)*
WP3.2/ Elucidation of the role of disrupted function of glia and altered neuroglial interactions on the pathogenesis of NDDS *Lead: dr. Pivoňková*	1. Description of the functional properties of astrocytes and oligodendrocyte lineage cells in NDD (*Dr. Anderová)*
	2. Identification of the common mechanisms of altered intracellular signaling-induced changes in glial cells in NDD and neurodegenerative diseases *(Dr. Pivoňková)*
	3. Exploration of the role altered glial function on the neuronal activity in the pathogenesis of NDD *(Dr. Pivoňková)*
WP3.3/ Clarification of the role of microtubular deregulation in the pathogenesis of neurodevelopmental disorders, brain development, and cortical malformations *Lead: dr. Balaštík*	1. Identification of microtubule-associated gene variants in patients with epilepsy and malformations of cortical development *(Dr. Laššuthová)*
	2. Functional characterization of the microtubule-associated gene variants in a single molecule level *(Dr. Balaštík)*
	3. Identification of the effect of microtubule-associated gene mutations on neuron growth and cortical development *(Dr. Lánsky)*
WP3.4/ Definition of the significance of the neurodegenerative processes in the pathogenesis and progression of neurodevelopmental disorders *Lead: dr. Pail*	1. Characterization of the relationships between neurodegeneration-associated proteins, clinical outcomes, and electrophysiological profile in NDD model and patients *(Dr. Pail)*
	2. Identification of specific miRNAs involved in the neuroinflammation and neurodegeneration associated with NDDs *(Prof. Brázdil)*
	3. Identification of novel specific histopathological biomarkers, electrophysiological and neuroimaging patterns with possible clinical consequences *(Dr. Kubová)*

WP3.5/ Identification of structural and functional rearrangement of brain network in neurodevelopmental disorders *Lead: prof. Otáhal*	1. Development of new MRI protocols and analyses to improve detection of structural rearrangement in NDDs *(Prof. Otáhal)*
	2. Elucidation of the mechanisms responsible for altered cerebral metabolism and brain perfusion in NDDs *(Prof. Otáhal)*
	3. Development of rapid structural, functional, and metabolic screening methods for diagnostics and drug screening for personalized treatment of NDDs *(Prof. Otáhal)*
WP3.6/ Elucidation of the role of disrupted placenta-axis in the increased risk of NDDs and neurodegenerative disorders *Lead: Prof. Staud*	1. Characterization of the impact of prenatal disruption of the placenta-brain axis on placental mTOR signaling and neurodevelopment *(Prof. Staud)*
	2. Elucidation of the placenta-brain axis disruption on NDD development *(Prof. Staud)*

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FOCUS AND RESEARCH OBJECTIVES

Our research focuses on the properties of glia and its function in the pathophysiology of central nervous system disorders, such as focal cerebral ischemia, amyotrophic lateral sclerosis, Alzheimer's disease, epilepsy, and tumorigenesis. In particular, using genetically modified mouse strains and new technologies specifically designed for the research of glial cells, we study the role of astrocytic ion and water channels in cerebral edema and post-ischemic regeneration. In addition, we investigate the role of Wnt signalling pathway in NG2-glia in neurogenesis and gliogenesis following ischemic brain injury.

Research objectives:

- *Astrocyte dysfunction in focal cerebral ischemia and neurodegenerative disorders*
- *Neurogenic potential of NG2 glia*
- *Mechanisms of astrocyte – microglia interactions under pathological conditions*
- *Novel technologies and approaches to study the role of astrocytes in brain function and dysfunction*

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FOCUS AND RESEARCH OBJECTIVES

- **Biomarkers, risk factors and modifiers of neurodegeneration with cognitive impairment**
  - **Define blood and CSF biomarkers in neurodegeneration**

The pathogenesis of different neurodegenerative diseases, such as Alzheimer's, Parkinson's, and Huntington's disease, share several common features. Among the proteins involved in neurodegeneration and possibly biomarker candidates, we have growth factors (BDNF, VEGF, IGF-1), degenerative factors (GFAP, NfL), and inflammatory mediators. In patients with AD and its precursor form MCI we have recently found that the serum levels of the enzymes regulating the synthesis of plasmin in CNS (tPA and PAI-1) are altered in patients with AD dementia type as compared to cognitive healthy subjects Interestingly, the synthesis of many mentioned biomarkers can be influenced by plasmin. Thus, the project aims to study the cellular and molecular mechanisms underlying neurodegeneration. We will try to identify new biomarkers and the analysis of circulating biomarkers will be correlated with the severity of the metabolic condition and the appearance of cognitive impairment/neurodegeneration to identify early markers of the disease.

Research objectives:

- *to obtain precise and complete characterization of trophic and degenerative factors and PAI-1/tPA changes during the development of neurodegenerative processes and define their role as biomarkers*
- *to validate the use of peripheral levels of the proteins involved in this pathway to characterize disease stage and disease outcome in neurodegeneration by association with neuropsychological and neuroimaging data*

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FOCUS AND RESEARCH OBJECTIVES

Microtubule (MT) deregulation is an important factor in pathogenesis of multiple neurodevelopmental disorders. We have recently shown that MT-associated protein CRMP2 specifically alters MT dynamics, brain development and that its disfunction in vivo leads to histological and behavioral changes associated with autism spectrum disorder. In our current projects we aim to uncover the molecular mechanisms through which microtubule associated proteins regulate neuron migration, axon growth and guidance, synapse refinement and brain connectivity formation. To reach this goal we use compartmentalized primary neuron cultures, generate and analyze mouse models of full gene deficiency (knockout mice), or specific gene upregulation in some cortical neurons (by the in-utero electroporation).

Research objectives:

- *the role of microtubules and microtubule associated proteins in neural development - particularly axon guidance, synapse formation and refinement*
- *analyzes conformational regulation of microtubule associated proteins during neural development*
- *studies deregulation of microtubule associated proteins in the pathogenesis of neurodevelopmental disorders – in particular autism spectrum disorder and epilepsy.*

SELECTED PUBLICATIONS

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Maimon R, Ankol L, Gradus Pery T, Altman T, Ionescu A, Weissova R, Ostrovsky M, Tank E, Alexandra G, Shelestovich N, Opatowsky Y, Dori A, Barmada S, Balastik M, Perlson E. A CRMP4-dependent retrograde axon-to-soma death signal in amyotrophic lateral sclerosis. EMBO J. 2021 Jun 30:e107586.

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FOCUS AND RESEARCH OBJECTIVE

- **Impact of COVID-19 on brain functions: Central mechanisms of post-COVID syndrome**
  - **Describe impact of COVID-19 on neural plasticity and brain function**

Our research group is primarily focused on the consequences of SARS-CoV-2 virus infection. A significant proportion of patients infected with the virus exhibit a range of persistent symptoms even after the resolution of acute COVID-19 disease, a condition often referred to as the post-COVID syndrome. Estimates of the prevalence of this condition vary, but it appears to be high, with some estimations of global prevalence being as high as 0.43.

This syndrome has the potential to pose a significant burden for both the quality of life of patients and healthcare systems. A high prevalence of neuropsychiatric symptoms has been reported, and there is a possible association with a higher risk of psychiatric or neurodegenerative disorders after SARS-CoV-2 infection.

We believe that neuroimaging is an optimal instrument to describe the biological substrates of this affliction. In our longitudinal study, we are using a multi-modal neuroimaging and electroencephalographic protocol, alongside cognitive testing and clinical assessment, to explore several possible pathologies proposed to underpin this syndrome.

The overall aim of this study is to describe the impact of COVID-19 on neural plasticity and brain function. The objectives of the study are as follows:

Research objectives:

- *To delineate structural, microstructural, and functional neuroanatomical signatures of the post-COVID-19 condition based on MR imaging, EEG-derived large-scale network characteristics, and cognitive parameters.*
- *To investigate the course of the post-COVID-19 condition, associated MRI-derived cerebral structural and functional changes, EEG-derived parameters, cognitive performance, and neuropsychiatric alterations.*
- *To determine the relationship between brain morphology, function, and the severity of the symptoms associated with the post-COVID-19 condition.*
- *To evaluate factors related to acute COVID-19 or its treatment and their influence on the manifestation of the post-COVID-19 condition*
- *To evaluate factors related to acute COVID-19 or its treatment and their influence on the manifestation of the post-COVID-19 condition*

SELECTED PUBLICATIONS

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FOCUS AND RESEARCH OBJECTIVES

- **Biomarkers, risk factors and modifiers of neurodegeneration with cognitive impairment**
  - **Develop and validate a comprehensive neuropsychological battery for diagnosis of cognitive impairment in Parkinson's disease**

Test robustness of established PD-MCI criteria to variation in selected measures:

Established PD-MCI criteria posit a neuropsychological battery consisting of ten measures grouped to five domains. The choice of test measures and their assignment to domains is quite liberal and allows for high number of permutations that can be used to operationalise PD-MCI. In the aim 1, we will use existing data set of N > 100 de novo PD patients and N > 100 advanced PD patients assessed by a comprehensive neuropsychological battery to assign PD-MCI status to patients based on all allowed permutations of test scores from the battery and compare and contrast patients' PD-MCI status across permutations. We will also vary the threshold used to assign PD-MCI and compare PD-MCI status derived from the battery with PD-MCI status based on cognitive screening (MoCA test). The aim is to establish invariance of the PD-MCI criteria to the precise operationalisation used for their calculation.

Evaluate psychometric properties of PD-MCI battery:

The psychometric properties such as factor structure or internal consistency of PD-MCI batteries are usually neither assessed nor discussed. In this project, we will used above mention data set to evaluate psychometric properties of PD-MCI battery in PD patients via item response theory (IRT) tools such as confirmatory factor analysis (CFA).

Explore possible whole-brain anatomical and functional connectivity mechanisms of cognition in PD:
Building on evaluating robustness and reliability of the PD-MCI neuropsychological battery (evaluated in Aims 1 and 2 respectively), we will explore possible mechanisms underlying patient-specific cognitive profile by predicting patient-specific cognitive data from patient-specific MRI-derived anatomical and functional connectivity measures.
Assess depression, anxiety, personality and everyday activities changes in PD patients treated with STN DBS:
To evaluate affective (anxiety and depression) and personality traits changes including everyday activities after STN DBS in PD, longitudinal retrospective data in a cohort of advanced PD patients will be analyzed using IRT. Employing IRT techniques will allow for a more robust characterization of affective and personality changes after STN DBS compared to the traditional use of sum score. Item-level changes of affective and personality variables after STN DBS will be related to clinical characteristics, medication levels and changes of thereof, active electrode locations and MRI-based structural connectivity of DBS electrode with cortical areas.

- **Neuromodulation in the treatment of cognitive impairment in neurodegeneration**
    - **Evaluate the effects of low-frequency DBS of ventromedial STN for cognitive symptoms of PD**

An intervention based on low-frequency STN DBS (low-frequency STN theta oscillations (5–12 Hz) within the STN) will be developed and experimentally tested to alleviate cognitive symptoms of PD. A low-frequency theta rhythm stimulation will be delivered to the ventromedial part of STN DBS to positively influence cognitive performance while at the same time stimulating with high frequency (~ 130 Hz) in the dorsolateral STN to achieve optimal motor improvement (Lee et al., 2021; Solomon et al., 2017). Based on prior research, the cognitive functions tested with this stimulation setup will include verbal fluency and planning. The intervention will be tested on a prospective sample of PD patients treated with STN DBS.

Research objectives:

- *to describe cognitive, affective and personality consequences of PD-specific brain alterations*
- *to design and evaluate an intervention to alleviate cognitive symptoms in PD*
- *to evaluate the effectiveness of simultaneous high-frequency DBS to dorsolateral STN for motor symptoms and low-frequency DBS to ventromedial STN for cognitive symptoms of PD*

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FOCUS AND RESEARCH OBJECTIVES

Individual brain sensing: a key step in adaptive deep brain stimulation

Electrophysiological studies are crucial for the evolution of deep brain stimulation (DBS) therapy. Adaptive deep brain stimulation (aDBS) based on electrophysiological symptom-specific markers has been recently introduced into the clinical practice. aDBS is an intermittent stimulation reflecting the patient's actual needs. The main motivation behind this "smart" stimulation is the minimization of treatment side effects by providing only the necessary stimulation required. The success is dependent on the quality of marker, which reflects causal mechanisms of the underlying pathology. Advanced analysis of electrophysiological data may reveal subject-specific oscillatory relations in target area linked to actual clinical state, individual symptoms and disease phenotype. Detected Local Field Potential (LFP) spectral patterns will allow individualization of the therapy and will play a key role in the new era of aDBS.

Research objectives:

- *determine optimal contact for DBS based on lead location, LFP and structural connectivity.*
- *define individual spectral patterns in LFP as a potential input signals for aDBS.*
- *evaluate alterations in LFP spectral patterns in longitudinal examination in the context of adverse effects of DBS and disease progression.*
- *identification of LFP patterns related to different phenotypes of Parkinson's disease.*

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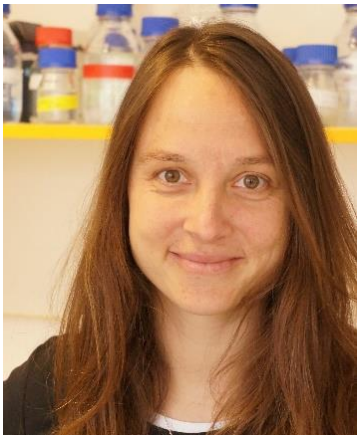

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FOCUS AND RESEARCH OBJECTIVE

- **Basic research leading to novel therapies**
  - **Using stem cells for disease modeling: From studying AD-causing pathogenic mutations to developing a pipeline for functional experiments and therapeutic targets discovery**

During the past decade, induced pluripotent stem cells (iPSCs) have been widely used for disease modeling in vitro, as they can be derived from patients, differentiated to disease-relevant cell types, and subsequently used to test mechanisms of disease initiation and progression, evaluate functional roles of genetic mutations, and screen for potential drugs. Especially in neuroscience, robust protocols for their differentiation towards mature 2D neurons and 3D cerebral organoids have been established, enabling truly complex studies on a human-relevant model system. Numerous of these studies have already provided new clues about neuronal development, physiology, and functional changes in a plethora of neurological diseases, including neurodegeneration (Barak et al., 2022; Lancaster and Huch, 2019). Specifically, in the field of Alzheimer's disease (AD), studies show that iPSC-based system faithfully recapitulates the AD pathogenesis in vitro (formation of Aβ plaques and P-TAU) and can be used to study mechanisms and pathways leading to the onset and progress of AD (Caldwell et al.; Ghatak et al., 2019). Additionally, iPSC-based technologies could provide significant clues not only to the cellular and molecular changes coupled to existing AD pathology but also to the initial steps leading to its development. Importantly, investigating functional aspects of the disease onset could potentially lead to identifying relevant targets for future therapies.

Our group focuses on modeling neural differentiation in vitro using human pluripotent stem cells. We aim to understand mechanisms of neural induction and differentiation and use this knowledge to model/treat CNS-related diseases. We currently use numerous neuronal models derived from human pluripotent stem cells, including 2D neurons, neural stem cells, and 3D cerebral organoids, and focus our studies on Alzheimer's disease and Glioblastoma. Specifically, we aim to understand the molecular basis underlying the initiation of Alzheimer's disease pathology development.

Research objectives:
The general objective of this project is to establish a working pipeline for modeling neurodegeneration diseases using iPSCs, followed by their functional phenotyping to identify potentially relevant targets for pharmacological interventions and proof-of-concept studies.
To fulfill this general objective, we propose the following specific aims:

- *Create iPSCs with AD-causing pathogenic mutation*
- *Differentiation and aging of iPSCs-derived 2D neurons and 3D organoids*
- *Phenotyping and functional experiments*

Importantly, the iPSC-based technology can be used to study any neurological disease. We thus envision that our established pipeline will be applied to other areas of neurodegeneration and used across numerous teams in Brno and Prague for studying, e.g., epileptogenic mutations, NMDA-related excitotoxicity, ALS, etc.

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FOCUS AND RESEARCH OBJECTIVE

- **Cortical excitability – from molecular to behavioural levels**

We explore the manifold factors that modify cortical excitability by performing multimodal and multilevel investigations. In doing so, we can uncover the basic neural mechanisms underlying several psychophysiological phenomena (e.g., déjà vu) and advance our understanding of pathological mechanisms behind the development of various neuropsychiatric diseases (e.g., epilepsy and Alzheimer´s disease).

- **Large-scale neural network dynamics underlying human behavior**
  - **Principles of neural connectivity underlying normal and pathological brain processing**

Further we compare the architecture of structural and functional connectivity networks and model their interrelationships. We will also investigate changes in neural connectivity in terms of developmental, physiological and pathological neuroplasticity. The findings of these studies will contribute significantly to our knowledge of neural "wiring" in the healthy and diseased brain. Furthermore, by characterising the nature of network reorganisation in neuropsychiatric conditions, these studies can identify useful early biological disease markers.

Research objectives:

- *To improve our understanding of the transition from normal to pathological cortical excitability in the human brain*
- *To understand principle mechanisms in neural connectivity in the adult and developing brain*

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FOCUS AND RESEARCH OBJECTIVE

- **Basic research leading to novel therapies**
  - **Unravel biological function of APOE proteins and test their potential correction by small molecules**

We will aim to understand the effect of point mutations in APOE molecules on the onset of Alzheimer's Disease. We will conduct detailed biophysical, biochemical and structural experiments of APOE3 and APOE4 proteins to study their oligomerization, lipidation and interactions with Abeta peptide. The objective will be to better understand the effect of single-point mutation on the structure and biology of APOE molecules, which represent one of the strongest risk factors of Alzheimer's Disease. Single-point mutants of APOE will be prepared and studied using various biochemical and biophysical techniques. We will study the effect of small molecules – so called correctors – on the aggregation of APOE and Abeta using both theoretical and experimental approaches (protein level, cell level and organoid level). Virtual screening of molecules representing brain metabolome will be conducted with the structure of APOE4 protein, and the best binders will be re-scored by neural network ad quantum mechanical calculations. We will employ several different libraries of small molecules during the screening: (i) FDA/EMA-approved drugs which could be possibly be repurposed for AD, (ii) aging mouse metabolome (complete metabolome at different ages), (iii) human metabolome, (iv) human lipidome. The top hits obtained by using in silico screening will be ordered and tested for anti-aggregating properties with APOE4. New methodology for this testing will have to be developed and established in our laboratory. The compounds showing aggregation-supressing properties will be studied into greater detail. Through all these activities, we will gain new knowledge about the biological function of APOE proteins and their potential correction by small molecules.

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FOCUS AND RESEARCH OBJECTIVE

- **Basic research leading to novel therapies**
  - **Identification of specific pharmacological modulators of tau spreading for Alzheimer's disease preclinical studies**

Intracytoplasmic aggregates of tau are pathological hallmarks of tauopathies – a group of neurodegenerative disorders (NDD). Pathogenic tau develops early in patients' brains before the development of major brain histopathological changes and spreads between interconnected neurons in a prion-like manner. Two amyloid motifs and cysteine residues in the repeat domain of tau protein are critical for prion-like strain formation and their spreading. To date, tau-based drug discovery efforts have focused on reducing tau levels or preventing post-translational modifications, but prion-like spreading has recently gained attention as a therapeutic target for tauopathies. The main aim of this WP is to identify bioactive substances against tau spreading for preclinical research using peptide-based models of tau for drug screening, cell models of tau aggregation and human NDD iPSC-derived neuronal cultures.

Research objectives:

- *To screen two chemical libraries of approved drugs (drug repurposing) and new chemical entities from the IMTM compound collection (>120k compounds) by a peptide-based high throughput-compatible tau aggregation assay.*
- *How the identified hits affect the biochemical, biophysical and structural properties of tau, crucial for aggregation and propagation, will be performed using biochemical and biophysical approaches and atomic force and transmission electron microscopy.*
- *Molecular dynamics simulations will be performed to identify if the hits interact with amyloid*

motifs or cysteine residues in tau and the potential mechanisms of anti-amyloidogenic effects

- *Whether the identified hits abolish the formation of toxic, pathological prion-like aggregates will be examined by cellular seeding assays using human tauopathy post-mortem brain samples, tau-expressing cells and neural cultures derived from patient iPSCs to model tauopathy.*

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FOCUS AND RESEARCH OBJECTIVES

Parkinson disease (PD) is the second most frequent neurodegenerative disorder, affecting more than 6 million of people globally. Up until now, clinical trials in PD examining substances that were efficient in preclinical animal models or cell cultures did not show any disease modifying effect in human patients. The failure of the latter studies could be due to lack of reliable biomarkers of disease progression measuring small disease modifying effect and because neuropathological changes in PD begin decades before patients manifest motor symptoms while it may be too late to interfere with the neurodegenerative process that is already too far advanced.
We aim to longitudinally follow patient cohorts with de novo PD and prodromal synucleinopathies to find and validate new biomarkers of prodromal and early-stage neurodegeneration associated with abnormal alpha-synuclein aggregation. The approaches to diagnose prodromal stage synucleinopathies are based on enhancing detection of subjects with known risk markers for prodromal PD such as hyposmia, REM sleep behavior disorder, mild motor disorder or substantia nigra hyperechogenicity on transcranial ultrasound examination. We will develop methodologies for diagnosing prodromal PD using social media marketing tools as well as take advantage of existing aging cohorts. Our ultimate goal is building a solid basis for detecting suitable patients and finding reliable endpoints for future neuroprotection trials.

Research objectives

- *Find reliable biomarkers of prodromal and early-stage synucleinopathies*
- *Evaluate the feasibility of population screening of prodromal neurodegeneration*

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FOCUS AND RESEARCH OBJECTIVE

- **Biomarkers, risk factors and modifiers of neurodegeneration with cognitive impairment**
  - **Use of proteomic approach indetify novel biomarkers in neurodegenerative diseases: Analysis of proximal fluids: tears**

The diagnosis of neurodegenerative disorders such as Parkinson's disease (PD) is still challenging, and biomarkers could significantly improve diagnostic accuracy, early detection and thus targeted intervention. In Alzheimer disease (AD), frontotemporal dementia (FTD), and dementia with Lewy bodies (DLB), many of these disorders include a combination of different proteinopathies and, therefore in vivo biomarkers derived from proteomic analysis of biofluids are crucial for more accurate diagnostics in the course of disease development and might allow detection during the prodromal or even pre-clinical stages of the disease. The current trend of biomarker research is to minimise the invasiveness of sampling biological materials and, at the same time, increase the specificity of the biomarker for the target tissue. This leads researchers to focus on body fluids such as saliva, exhaled breath condensate, urine, tears etc. Currently, there are only two proximal body fluids where biomarkers of neurological diseases are being widely searched: CSF and blood or serum. However, CSF sampling is invasive and often poorly tolerated while blood supplies the whole body. Interestingly, human tears are well accessible and their sampling is non-invasive. Their additional advantage is that they are proximal and phylogenetically closely related to the brain. Pilot analysis of human tears performed by our group has shown the presence of proteins frequently expressed

in brain or neuronal tissues. To our knowledge, there has been no systematic evaluation of the tear proteins across various neurodegenerative disorders.

Research objectives:

- *To collect biological samples from patients with neurodegenerative disorders or the different risk groups such as Parkinson's disease (PD) and Alzheimer's disease (AD) and corresponding control samples, age and sex-matched, undergoing clinical examination for other reasons.*
- *To prepare a database of patient's samples and their clinical data in a specialised ClinData database proprietary developed at the IMTM.*
- *To perform a proteomic discovery analysis of tears versus other biomaterials of patients from particular disease/therapeutic groups and controls – analysis of the patient samples and corresponding control samples. To identify significantly altered protein profiles in correlation with clinical data, selection of proteins distinguishing control and patient samples.*
- *Development of the panel of the protein biomarkers based on the results of the discovery phase and on the currently published data in the literature.*

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FOCUS AND RESEARCH OBJECTIVE

- **Biomarkers, risk factors and modifiers of neurodegeneration with cognitive impairment**
  - **Define immune signature of prodromal dementia with Lewy bodies**

The main aim of this WP is to perform a detailed evaluation of immune phenotype and to screen for aging-related markers at cellular and humoral level in patients suffering from neurodegenerative disorders. These results will aim to identify potential diagnostic and stratification markers, or phenotype profiles associated with disease-specific neurodegenerative changes. In combination with the results obtained from clinical screening methods, this will help us to design a high-throughput tool for patient risk stratification, which would enable proactive clinical management of patients at a high risk of neurodegeneration.

- **Impact of COVID-19 on brain functions: Central mechanisms of post-COVID syndrome**
  - **Describe changes in immune phenotype in the COVID19 patients with the post-COVID syndrome**

The main aim of this WP is to evaluate the impact of SARS-CoV-2 infection in individuals suffering from post-COVID syndrome on the immune system, and to search for predictive markers enabling patient risk stratification and early intervention. Other aims are to perform an in-depth analysis of T-cell phenotype changes following SARS-CoV-2 infection. This immunophenotype will be correlated with COVID19-induced long-term adverse effects.

- **Microbiome in neurodegenerative disease with cognitive impairment**
  - **Validate the use of iPSC derived intestinal organoids as a tool to study gut-brain axis and molecular mechanisms of host-pathogen and microbiome interaction in intestinal tissue**

Within this WP we aim to use of human induced pluripotent stem cell-derived 3D gut organoids as advance model of mucosal tissue in order to: i) to identify capacity to produce mediators of gut-brain axis based on stimulation of different cytokines controlling microbiome and ii) to define differences of bacterial isolates to stimulate the gut organoids. The results will help to define important aspects of gut brain axis and how these interaction corelates with severeness of neuropathologies. This knowledge can also pave the road towards personalised medicine using patients derived organoids to screen or predict the role of the individual microbiome.

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FOCUS AND RESEARCH OBJECTIVE

- **Neuromodulation in the treatment of cognitive impairment in neurodegeneration**
  - **Develop hardware and protocols to perform Temporal Interference Stimulation (TIS) in both animal models and humans**

Neuroelectronics is the field of creating artificial electronic interfaces that are capable of communicating with the nervous system, either by recording electrical activity or by stimulating it. To improve neuroelectronic devices in clinical practice it is vital to create solutions which are more minimalistic and less invasive for the patient. We work on new methods for delivering electrical stimulation noninvasively to deep neural targets in a precise and safe way. In particular, our project focuses on developing the relatively new technique of temporal interference stimulation (TIS). This method aims to overcome the fundamental limitation of noninvasive electrical stimulation which is the high impedance of skin to the bandwidth of frequencies required for neurostimulation (1 – 200 Hz). TIS utilizes relatively high frequencies in the range > 1 kHz, where the impedance of skin and tissue is at least two orders of magnitude lower. In order to achieve stimulation, two or more high-frequency signals constructively interfere to create envelopes of lower frequency which are capable of stimulating tissue. This method carries great promise as it relies on fundamental principles of electrodynamics, simple and established hardware for transcutaneous stimulation, is fully noninvasive, and can target structures arbitrarily deep inside of the body.

Research objectives:

- *Develop a testing platform with stimulation and recording hardware for prototyping TIS in phantom models. These models are tissue-mimicking structures prepared by 3D printing, which are meant to imitate the electrical and mechanical properties of anatomical structures (in particular the human head). These structures allow advanced prototyping and quantification of temporal interference stimulation patterns in a nonbiological setting.*

- *Utilize finite element computer modeling to predict the stimulation that can be achieved by TIS.*
- *Perform TIS experiments on low-cost and ethically facile animal models, namely invertebrates like insects and annelids. These models allow testing of new stimulation protocols with evaluation of electrophysiological outcomes in a way that avoids ethically and economically demanding animal models.*
- *Develop and manufacture custom cutaneous electrodes for human use of TIS, namely in the application of treatment of sleep apnea by hypoglossal nerve stimulation, and vagus nerve stimulation for treatment of chronic inflammatory conditions.*

Design and fabricate custom electrical stimulation hardware to deliver TIS using battery-powered integrated devices that can be used by patients outside of the clinical setting. At present, TIS is done using bulky and complicated clinical stimulators driven by laboratory electrical signal generators. To bring this solution to patients at home, an integrated and miniaturized solution is needed.

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FOCUS AND RESEARCH OBJECTIVES

Neurodegenerative proteinopathies (NDPP) like Alzheimer and Parkinson disease are defined by accumulation of pathologically folded specific proteins in the brain and other tissues of affected patients. Recently, it was demonstrated that different types of NDPP can be caused by the same pathological protein in different pathological conformation. Early diagnosis of NDPP is difficult and there is a pressing need to discover reliable biomarkers allowing laboratory confirmation of clinical diagnosis and populational screening. Our laboratory explores prion-like behavior of misfolded pathological proteins for their specific and ultrasensitive detection in different types of patient samples. We plan to utilize our experience with Real-time quaking-induced conversion (RT-QuIC) assay for prions in the development of the assay modifications for synucleionopathies and tauopathies and investigate their diagnostic potential.

Research objectives:

- *Increase our understanding of the fidelity of amyloid seed induced conformational change and aggregation of NDPP specific proteins. Evaluate if the conformational signature of pathological seed can be traced in the structure of aggregated product of RT-QuIC reaction and utilized to improve diagnostics of NDPP. Study the effect of the aggregation conditions on structure of resulting amyloid fibrils.*
- *Develop and validate variants of RT-QuIC assay for synucleinopathies, tauopathies and prion diseases utilizing clinically relevant patient samples. In collaboration carry out retrospective and prospective studies to confirm their diagnostic potential. Contribute to the implementation of RT-QuIC assay into routine clinical laboratory diagnostic practice*.

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FOCUS AND RESEARCH OBJECTIVES

- **Basic research leading to novel therapies**
  - **Study chronobiology of Alzheimer's disease in an animal model**

The main objective of this WP is to uncover the bidirectional relationships between the progression of Alzheimer's disease and circadian system disruption.

Research objectives:

- *Compare the effect of different types of circadian disruption on the progression of AD-like neurodegeneration and behavioral impairments*
- *Investigate the effect of idiopathic disruption of sleep pattern on neurodegeneration and behavioral impairment progression*
- *Examine the therapeutic potential of circadian synchronization enhancement via pharmacological and environmental drivers*

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FOCUS AND RESEARCH OBJECTIVES

The Department of Neurochemistry was established in 2018 to conduct cutting-edge research on regulating NMDARs in mammalian neurons under normal and pathological conditions. Specifically, we study the molecular mechanisms that regulate (i) the surface numbers of NMDARs, including their maturation in the endoplasmic reticulum and transport across the Golgi apparatus, and (ii) the surface mobility and localization of NMDARs in synaptic and extrasynaptic regions of mammalian neurons. We are also studying (iii) the functional impact of selected pathogenic variants in the genes encoding the GluN subunits of NMDAR and mTOR that are associated with the development of epilepsy, and (iv) we are developing pharmacological modulators with unique mechanisms of action at NMDAR. Our findings contribute to the understanding and future therapy of disorders associated with abnormal regulation of NMDARs, including epilepsy and Alzheimer's disease.

Research objectives:

- *trafficking of NMDA receptors (NMDARs)*
- *pathogenic variants in NMDARs and mTOR associated with epilepsy*
- *novel pharmacological drugs*

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FOCUS AND RESEARCH OBJECTIVE

- **Biomarkers, risk factors and modifiers of neurodegeneration with cognitive impairment**
  - **Sex differences in brain structure and biomarkers in Alzheimer's disease**

The heterogeneity of Alzheimer's disease presents a burden in early diagnosis, prognostication and treatment finding strategies. Our aim is to explore sex differences in diverse cohorts to evaluate sex as a source of heterogeneity in AD biomarkers, including more novel modalities such as digital biomarkers. Our main data source is the Czech Brain Ageing Study, a longitudinal prodromal-AD-focused cohort with multimodal data.

The major aim is to expand the current knowledge on sex differences in AD biomarkers (structural, metabolic or cognitive) in different stages of AD, to enable utilization of precision medicine approaches in AD diagnostics, and to contribute to disentangling the pathophysiologic background of sex differences in AD. In addition to traditional biomarkers, sex differences will also be explored in alternative biomarkers, such as digital biomarkers.

Secondary aims are to promote and expand international collaboration in the study of sex differences, and advocate for the study of sex differences within Czech and international communities.

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FOCUS AND RESEARCH OBJECTIVES

In the project, we focus on three main points: development, design and synthesis of chelators of biologically important metal ions, design, development and preparation of molecular structures with polyphenols, design, development and preparation of nano- or microformulations of drugs and their validation. From the point of view of medical applications, we focus on neuroprotective and adjuvant molecular systems and mixtures. Our laboratory has a unique RD pipeline in medicinal chemistry and experience in transitioning to a commercial partner

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FOCUS AND RESEARCH OBJECTIVES

- **Basic research leading to novel therapies**
  - **Study the interaction of neuroactive steroids with muscarinic receptors to enhance cholinergic signaling**

We are determining basic pharmacological parameters of currently available neuroactive steroids at M_1 muscarinic receptors by radioligand binding and functional experiments to establish a basic structure-activity-relationship.

Research objectives:

- *Delineation of the interactions of cholesterol and neuroactive steroids with muscarinic receptors as a pharmacological goal of enhancing cholinergic signalling that is weakened in neurodegenerative processes including AD. To gain new knowledge on the allosteric modulation of muscarinic receptors by cholesterol and neuroactive steroids for the structure-guided design of positive allosteric modulators of M_1 muscarinic receptors.*

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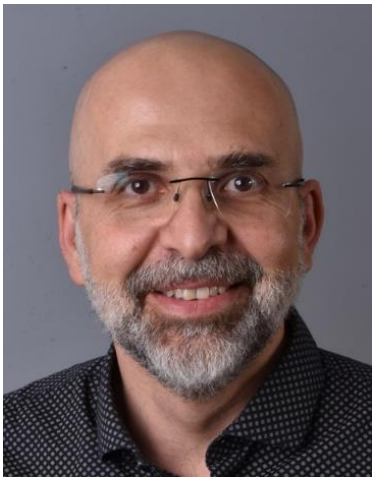

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FOCUS AND RESEARCH OBJECTIVES

Deep brain stimulation (DBS) is an effective therapeutic modality for various movement disorders and a promising option in several neuropsychiatric conditions. However, clinical approaches do DBS programming remain relatively unchanged compared to initial protocols, despite the recent developments in complex lead designs and increased stimulation field shaping abilities. DBS programming currently entails largely manual trial-and-error adjustments of settings based on patient responses. Nonetheless, the vast number of theoretically possible configurations with the emergence of increasingly complex technologies will soon make manual programming infeasible. Even the full evaluation of the current multi-segmented directional electrodes is associated with substantial time burden for the clinician and patient and is unlikely to fully capitalize on directional steering abilities and neuroanatomical nuances of precise DBS lead positioning to yield optimal parameter settings.

To meet this clinically clearly defined need, a number of software packages and approaches have been published to visually guide clinicians, to provide information on the extent of area stimulated and lately also on pathways activated by various stimulation settings. Nonetheless, these studies usually lack sufficient cohort sizes and clear confirmation of relationships between the activation of particular pathways and clinical outcomes in subsequent follow-up to truly provide clinically implementable, individualised, patient-specific recommendations as a guide for clinical programming sessions.

Research objectives:

- *Define the characteristics of structural and functional connectome for clinically effective DBS and for adverse effects in cognitive, behavioural, motor, or other domains*
- *Develop individualised, multimodal, connectome-driven approach to DBS programming to capitalize upon advances in DBS lead design and imaging*
- *Evaluate non-standard DBS parameters to address non-motor symptoms in Parkinson's disease, both clinically and using functional imaging*
- *Find preoperative markers associated with better outcome*

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FOCUS AND RESEARCH OBJECTIVES

- **Neuromodulation in the treatment of cognitive impairment in neurodegeneration**
  - **Describe mechanisms of memory impairments under neural oscillations disturbances in the hippocampal system using invasive stimulation in an animal model**

Besides the characteristic neuronal loss, the human neurodegenerative disorders, such as Alzheimer's disease or other types of dementia, are as well associated with abnormalities in neural oscillations. Neural rhythms in theta (6-12 Hz) or gamma (25-140 Hz) frequency ranges are dominant oscillations in the hippocampal circuitry that is essential for human declarative memories and animal spatial orientation. Because neural oscillations provide a temporal frame for the neural information processing and information flow across distinct brain areas, their alterations might account for functional disturbations such as memory impairment even before the actual loss of the neural cells. The range of differences can be expressed in reduced oscillatory power, in the frequency shift or both. Despite the role of rhythms in neural computation receives an intensive attention, the mechanisms of how the impaired oscillations affect the neural information processing in the brain memory circuits is largely unknown. The recurrent character of hippocampal (and neocortical) autoassociative networks tends to self-stabilize the memory patterns which might result in an inflexibility in retrieving memories. We recently identified that the network memory states show a periodic reset in theta rhythm pace that probably account for the flexibility of fast memory retrieval in response to a change in the network sensory inputs. We suggest that alleviation of theta rhythmicity that can be seen in Alzheimer's disease and other dementias might account for the cognitive inflexibility as the network memory state under weakened theta-based resetting mechanism is tending to get stuck. Such a mechanism might account for memory disturbations even during the absence of neurodegenerative anatomical changes.

Research objectives:

- *How is the neural information processing in hippocampus affected under reduced brain oscillations? Hippocampal and neocortical spiking activity is organized in various rhythmic modes that provide a temporal scaffold for effective information processing. Here we will reduce the dominant oscillation (theta. 9-12 Hz) in hippocampal system by silencing neural activity in medial septum and test how this manipulation affects effectivity of memory recall kinetics on the neural network level*
- *How the direct brain stimulation (DBS) in the theta range within the hippocampal memory system affects the spatial memory code processing in a models of dementia? Here we will use the DBS approach to reinstate the physiological cell activity*

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FOCUS AND RESEARCH OBJECTIVE

- **Microbiome in neurodegenerative disease with cognitive impairment**
  - **Define the role of the gut microbiome in the pathophysiology of dementia – translational research**

Dementia is not a disease; it is a syndrome characterized by decreased cognition, which is noteworthy enough to alter your daily functioning. The human body contains trillions of microorganisms, in gut microbes play a significant role in maintaining health and immune function. Recently it has been reported that they are also involved in neurodevelopment, modulating behavior by altering neurotransmitter levels, and are responsible for neurological disorders. Moreover, the research on dysbiosis of gut microbes and neurological disorders has rapidly increased in the last ten years. Now the term' Gut-brain axis' has broadened to 'microbiota-gut-brain axis,' evidencing the gut and brain connection is bidirectional and modulation of altered intestinal microbes might be the novel therapeutic approach for treating neurological disorders. A recent study reported that gut dysbiosis contributed to amyloid pathology. Furthermore, a meta-analysis study in Parkinson's disease patients suggested a significant alteration in gut bacteria producing short-chain fatty acids, resulting in pro-inflammatory status that could be linked to GI symptoms in PD.

Research objectives:

- *We aim to transfer fecal material from demented and non-demented Parkinson's disease patients to our well-established progressive intragastric rotenone mouse model.*
- *We want to study the effect of altered microbes on rotenone-induced alpha-synuclein accumulation induction using diffusion kurtosis imaging and immunohistochemistry, which will be later correlated with memory impairment.*

- *Further, we would like to perform metabolomics in the hippocampus and cortex after fecal material transfer from demented patients in rotenone-treated mice to check the alterations in neurogenesis and metabolites.*

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FOCUS AND RESEARCH OBJECTIVES

Computational neuroscience research group is focused on development of advanced methods for signal processing in neurology, study of the human brain electrophysiology and neurological diseases. Our ultimate aim is open-source and open-science development of advanced technologies and subsequent implementation of these tools into clinical practise in order to improve medical treatment, lower risk and reduce time of patient's hospitalization. Our group consists of biomedical engineers and neuroscientists and for many years collaborates with scientists, medical doctors, electrophysiologists and students from Brno University of Technology, Masaryk University, St. Anne's hospital in Brno and international centers: Mayo Clinic in Minnesota, USA and Montreal Neurological Institute and Hospital in Canada. Currently, our research is mainly focused on patients with pharmacoresistant epilepsy and patients with Parkinson's disease.

Research objectives:

Development of methods for automatic processing

- Development of automatic and semi-automatic tools for data quality assessment and pre-processing of extensive EEG recordings.
- Development of a multicentric database with prolonged recordings, which should allow for testing on bigger samples across different institutions.

Research and development of analytical methods

- Methods for broadband EEG signal processing - analysis of interictal epileptic discharges and high frequency oscillations (HFO).
- Connectivity and mutual interactions between anatomical structures of the human brain, analysis of the epileptogenic zone functional connectivity.

Application of developed methods in neurology

- The basic research of motor and cognitive processes.
- Analysis of the epileptogenic zone function, dynamics of epileptic seizures.
- Effectivity of deep brain stimulation (DBS).
- Machine learning models:
  - localization of the epileptogenic zone
  - prediction of surgical outcome in epilepsy surgery
  - seizure forecasting and seizure prediction
  - prediction of the effect of vagal nerve stimulation (non-invasive scalp EEG study).
- Implementation of the developed tools into clinical practise.
- Therapy: aimed estimation, selective micro ablations.

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FOCUS AND RESEARCH OBJECTIVE

- **Basic research leading to novel therapies**
  - **Validate CGMP production of mesenchymal stem cells for neurodegenerative diseases**

Normal MSC function is to migrate to areas of injury and participate in the reparative process. Both allogeneic and autologous MSC therapies are in development. Unlike most other allogeneic cell therapies in clinical development, allogeneic MSC therapies may be used without concomitant immunosuppression due to their paucity of MHC Class II proteins and decreased propensity to trigger an immune response. The precise mechanism by which MSCs may exert beneficial effects in neurological disease is still being elucidated, but it appears that multiple different mechanisms may contribute First, MSCs have been shown to secrete neurotrophic growth factors, including glial cell-derived neurotrophic factor (GDNF), vascular endothelial growth factor, and brain-derived neurotrophic factor (BDNF), which can be further enhanced under specific culture conditions. Neurotrophic growth factors have been shown to improve neuronal survival in a number of preclinical models of neuron injury, including ALS, PD, and MSA transgenic animals and nerve injury models. Second, MSCs strongly modulate the immune system and can aid wound healing, and this mechanism has been exploited in disorders such as graft versus host disease20 and Crohn's disease. From a neurodegenerative perspective, it has become increasingly recognized that neuroinflammation plays a significant pathomechanistic role. Neuroinflammation in this context is

defined as the negative contribution of non-neuronal cells (immune cells, glial cells, etc.) to neurodegenerative disease. While all of the details are not worked out, it is clear that activated microglia, astrocytes, and T-cells are able to interact and increase neuronal death due to proinflammatory and reactive oxygen species production. Interestingly, MSCs may be either anti-inflammatory or proinflammatory depending on the milieu within which they exist. When entering an inflammatory milieu (interferon-gamma, tumor necrosis factor-alpha), MSCs become anti-inflammatory wherein they secrete transforming growth factor-beta1, indoleamine-2,3-dioxygenase, and prostaglandin E2 and can convert macrophage/microglia from the pro-inflammatory M1 to the anti-inflammatory M2 phenotype. MSCs mediate their immunomodulatory effects via direct cell-cell interactions, but also have strong paracrine influences via secreted cytokines and growth factors. One of the key methods that MSCs secrete biological factors is via extracellular vesicles (EVs).

Alzheimer's disease (AD) is the most common cause of dementia. The typical clinical dementia syndrome associated with AD is that of a slowly progressive decline in memory appearing early in the clinical phase of the disease. The classic neuropathological features are neuritic plaques and neurofibrillary tangles. Central mechanism appears to be that of glial dysfunction with resulting deficiency of growth factors, especially BDNF and GDNF, which are critical for neuronal survival.

Research objectives:

- *validation of the preparation of clinical grade GMP produced MSCs suitable for the treatment of neurodegenerative diseases will be set up- using molecular biology approaches, the hypothesis whether MSC1 polarization leading to increase an anti-inflammatory cytokines production also positively affects the production of CNTF and BDNF will be verified.*
  The aim is to design MSCs and validate culture protocol leading to the maximization of the therapeutic effect of these cells in AD. Motivation Thee ability of MSCs to secrete neurotrophic factors may improve the cellular milieu and limit cell loss in the setting of this complex AD pathophysiology. In addition, MSCs' known immunomodulatory effects may limit the damage effects of activated glial cell related synaptic pruning and inflammation in general. MSCs also have the potential to deliver a healthy supply of mitochondria to the CNS thereby mitigating the impact of age and AD-related mitochondrial dysfunction.

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FOCUS AND RESEARCH OBJECTIVE

- **Microbiome in neurodegenerative disease with cognitive impairment**
  - Define relationships between microbiome composition and disease biomarkers and clinical outcome

Neurodegenerative diseases (NDs) of the brain are characterized by progressive and irreversible loss of neurons that develop insidiously and finally results in significant cognitive impairment (CI). The most common NDs with CI are Alzheimer´s disease (AD) and Lewy body dementias (LBDs) together with Parkinson´s disease (PD) dementia. These diseases represent the majority of all dementia cases and have devastating impact on patient´s life as well as their relatives. The etiology of NDs is still not fully understood. There is increasing interest in the role of human microbiome in development and progression of NDs. The metabolites and agents produced by gut, nasal and oral microbiota may induce changes in brain activity and this relationship is bidirectional, generally termed as gut- /nasal- /oral- brain axis. However, the mechanism of this interaction remains unclear, it is discussed the direct influence via peripheral nerves (e.g. vagal nerve, olfactory nerve, glossopharyngeal nerve); or indirectly via circulating agents that may alter immunology processes. Also, microbiota is capable to produce neurotransmitter-like proteins. The microbiome dysbiosis may lead to neuroinflammation and further induce pathological cascades resulting in amyloid/synuclein/tau aggregation in the brain. The modulation of human microbiota thus represents potential effective therapeutic mechanism to modify the course and progression of NDs as well as to reduce the risk of development of NDs.

Research objectives:

- *characterize the microbiota composition of the gut, the oral and nasal cavity in patients with AD and LBDs across the clinical spectrum (changes between mild and advanced stages of NDs), its dynamic changes over time (3y prospective longitudinal study) and the differences in microbiota between the amyloidopathies and synucleinopathies*
- *identify which microorganisms in the body may influence the brain processes (nasal, oral & gut–brain axis) and describe the possible pathological processes leading to brain activity alterations which could contribute to neurodegeneration, i.e. amyloid, synuclein or tau deposition (using mice disease models, gut organoid models, see in our other studies)*
- *to define the relationships between microbiome composition (taxonomic and functional activity) and disease biomarkers and clinical outcomes in patients with NDs; 4. Results of this study are planned to be used for preparation of interventional study with gut and oral probiotics as targeted microbiome-modulating therapy of NDs with CI.*

SELECTED PUBLICATIONS

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FOCUS AND RESEARCH OBJECTIVES

The laboratory focuses on developmental aspects of epilepsy, age-specific epilepsy treatments and safety of anti-seizure medications for developing brain. Using molecular, histological, electrophysiological and behavioral methods, we study mechanisms underlying ictogenesis, epileptogenesis and epilepsy related comorbidities in immature rodents. Also, in close collaboration with clinical epilepsy centers, we work to develop new diagnostic techniques for epilepsy. Beyond basic research, we work to a limited extent with the pharmaceutical industry to search for age-specific anti-seizure drugs and to ameliorate the potential adverse side effects of these drugs.

Research objectives

- *Age-specific mechanisms of ictogenesis, epileptogenesis and epilepsy-related comorbidities*
- *The long term impact of early life exposure to anti-seizure drugs on brain development*
- *Developmental pharmacology of classical and potential anti-seizure drugs*

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FOCUS AND RESEARCH OBJECTIVES

Our group focuses on the ictogenesis and long-term evolution of seizures in a mouse model of epilepsy due to focal cortical dysplasia (FCD). We use optogenetics and chemogenetics to specifically activate or inhibit selected neuronal populations to elucidate their role in the generation of seizures and other epileptic EEG phenomena such as high-frequency oscillations. Moreover, we study the long-term fluctuations in the seizure susceptibility of the mice using analyses of passive EEG markers of the brain dynamics and using active probing of the brain excitability.

Research objectives:

- *Mechanisms of ictogenesis and epileptogenesis*
- *Gene therapy of epilepsy*
- *Pathological brain oscillations*
- *EEG biomarkers of epilepsy*
- *Focal cortical dysplasia*
- *Long-term dynamics of seizures*

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FOCUS AND RESEARCH OBJECTIVES

The laboratory focusss primarily on the discovery and diagnosis of molecular genetic basis of severe childhood epilepsies: both caused by malformations of cortical development (MCD), especially focal cortical dysplasia (FCD), and epileptic encephalopathies caused by pathogenic variants in genes coding for ion channels and synaptic proteins. The team of NGL also investigates genetic causes of peripheral neuropathies, hereditary spastic parapareses, hereditary hearing loss and severe childhood-onset neurogenerative diseases.

Research objectives:

- *genetic causes of epileptic encephalopathies, focal epilepsies and malformations of cortical development, including focal cortical dysplasia*
- *genetic variability among epilepsy surgery patients and the effect of genetic causes on epilepsy surgery outcomes*
- *discovery of novel genetic causes of peripheral neuropathies, hereditary spastic parapareses, severe childhood-onset neurodegenerative diseases and hereditary hearing loss*

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FOCUS AND RESEARCH OBJECTIVES

Cytoskeletal networks form the internal dynamic scaffold of living cells essential for key cellular processes, such as cell division, cell motility or morphogenesis. Ensembles of cytoskeletal proteins self-assemble to drive these processes. Our aim is to understand the principles that underpin their collective action resulting in the generation of a coherent behavior of the cytoskeletal networks. Our main experimental strategy is bottom-up reconstitution of cytoskeletal networks from individual components in vitro. We use genetic manipulations, biochemical and biophysical methods and mathematical modelling. Central to our approach are imaging and force measurement techniques with single molecule resolution.

Research objectives:

- *molecular mechanisms of neuronal pathfinding*
- *contractility of actin networks and their anchoring to the plasma membrane,*
- *regulatory roles of neuronal intrinsically disordered, microtubule-associated proteins*
- *long-range intracellular transport*

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FOCUS AND RESEARCH OBJECTIVES

In 2021, based on continuous research activities centred on Neurodegenerative disorders, the Brain Bank in Czech Republic was founded as an institution of the Third Medical Faculty, Charles University, and Thomayer University Hospital in Prague. Its principal aim is to store and investigate tissue samples obtained during autopsy or biopsy from brains of clinically documented patients with different types of neurological and psychiatric diseases. The Brain Bank will also collect other biological tissue samples: cerebrospinal fluid, blood samples, bone marrow. Since autopsy is provided only in a limited number of patients with dementia and definite diagnosis of neurodegenerative disorders is based on neuropathological confirmation, the existence of the Brain Bank, awareness about its existence, autopsy and biopsy facilities but also the possibility of brain

donation by patients for research purposes can considerably increase both diagnostic accuracy and research potentials in neurodegenerative disorders including Alzheimer's disease, Parkinson's disease and other synucleinopathies, tauopathies or TDP-43 proteinopathies.

Research objectives:

- *Complex analysis of tissue samples in diagnosed neurodegenerative disorders based on concise correlations of clinical manifestation, neuroimage results, biomarker findings and neuropathological verification of causative misfolded protein deposits in brain tissue samples using whole spectrum of neuropathological methods.*
- *Retrospective investigation of protein biomarkers in cerebrospinal fluid samples and other tissues in correlation with the expression of pathologically conformed proteins in different brain areas and their impact on clinical manifestation of disease symptoms and signs. By this approach, we can established new useful tools for intravital diagnosis of neurodegenerative disorders. We will focus on close interdisciplinary collaboration and correlate neuronal cell loss in different brain areas with the distribution of misfolded protein inclusion on one hand, and the presence/absence of motor symptoms, oculomotor abnormalities and both the extent and proportionality of impairment in main cognitive domains (memory, language, visuospatial functions, gnostic and executive functions) paired with the evaluation of MRI signal abnormalities and different focal atrophy patterns taking into consideration results of cerebrospinal analysis for various proteinopathies (amyloid beta, tau, alfa-synuclein, 14-3-3 protein, neurofilaments, etc.)*
- *Detailed neurogenetic analysis of modifications in genes coding proteins directly involved in neurodegeneration and both known polymorphisms and variants of uncertain causal significance as well as epigenetic factor, which allows understand the possible genetic and epidenetic predisposition to the neurodegenerations. For the genetic analysis and correlations with histopathology and clinical profiles we will base on different panels for neurodegenerative disorders and massive parallel sequencing of next generation (NGS) for retrospective analysis of gene modifications in neurodegenerative disorders*

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FOCUS AND RESEARCH OBJECTIVE

- **Biomarkers, risk factors and modifiers of neurodegeneration with cognitive impairment**
  - **Design speech/voice and handwriting/drawing-based biomarkers supporting the diagnosis of prodromal dementia with Lewy bodies**

The main objective of this WP is to design a framework for the computer-aided prodromal diagnosis of DLB that will utilise acoustic analysis of speech/voice and computerised assessment of handwriting/drawing. The WP has the following specific aims.

Research objectives:

- *To identify digital speech/voice biomarkers facilitating the prodromal diagnosis of DLB*

Regarding the speech/voice biomarkers, the state of the art covers mainly the discrimination of healthy controls (HC), MCI and AD. In the frame of this WP, we will move further and bridge the knowledge gap associated with the acoustic analysis of DLB and its early diagnosis. We will find an optimal combination of speech/voice tasks and features that will provide good discrimination power, and that will also provide good clinical interpretability. The acoustic measures will be correlated with scores of neuropsychological assessments.

Hypothesis: Based on the state of the art in the acoustic analysis of dementia, we assume that mainly speech features quantifying prosody (more specifically speech rate and pausing – temporal features) will play a significant role in the prodromal diagnosis of DLB.

- *To identify digital handwriting/drawing biomarkers facilitating prodromal diagnosis of DLB*

We are going to explore the impact of computerised drawing/handwriting processing on the prodromal diagnosis of DLB. Similarly, to Aim 1, we will find an optimal combination of handwriting/drawing tasks and features that will provide good discrimination power. The outcomes of this part will be discussed in relation to the neuropsychological profile of a patient.

Hypothesis: We assume that cognitive tasks such as the pentagon copy test will enable us to effectively quantify visuospatial deficits. Analysis of in-air movement recorded during a sentence copy task will probably bring some valuable information as well.

- *To train machine-learning models enabling supportive prodromal diagnosis of DLB*

We are going to train and evaluate state-of-the-art machine learning models supporting the prodromal diagnosis of DLB. The models will be evaluated in terms of sensitivity and specificity and will be interpreted using feature importances or Shapley values. The models will be trained for each modality separately, as well as for both modalities together.

Hypothesis: We hypothesise that a model based on a gradient boosting algorithm will reach more than 70% sensitivity/specificity when fed by features from both modalities.

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FOCUS AND RESEARCH OBJECTIVE

- **Biomarkers, risk factors and modifiers of neurodegeneration with cognitive impairment**
  - Assess impact of lifestyle, social and spiritual wellbeing on brain health using multimodality imaging

The main aim is to investigate the associations among various life-style measures and behaviours (such as spiritual well-being, religiosity, physical activity, breathing, and positive psychology with measures of brain health derived from cross-sectional and longitudinal regional magnetic resonance imaging in older participants at risk of Alzheimer's disease (AD). The specific aims are as follows:

- To determine the associations between measures of spiritual well-being, institution-based spirituality and positive psychology with measures with measures of regional brain atrophy and functional connectivity over the time in participants within AD continuum
- To investigate the effect of physical activity on brain health by multimodality structural and functional brain imaging
- To investigate the effect of a diaphragmatic breathing versus regular breathing on brain structure, perfusion and connectivity in older participants at risk of AD

Research objectives:

The main objective of this WP is to uncover the bidirectional relationships between the progression of Alzheimer's disease and circadian system disruption. The specific objectives are as follows:

- *Compare the effect of different types of circadian disruption on the progression of AD-like neurodegeneration and behavioral impairments*
- *Investigate the effect of idiopathic disruption of sleep pattern on neurodegeneration and*

behavioral impairment progression

- *Examine the therapeutic potential of circadian synchronization enhancement via pharmacological and environmental drivers*

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FOCUS AND RESEARCH OBJECTIVES

By employing our state-of-the-art optophysiological hardware, we aim to describe the role of defined local neuronal populations in neocortical seizures, with emphasis on different interneuronal subtypes. Furthermore, we aim to test the previously postulated hypotheses suggesting possible subtype-specific roles of local interneuronal populations in focal cortical seizures, high-frequency oscillations, and ictogenicity of cortical malformations in an in vivo setting. The ultimate goal is to identify possible targets suitable for causal intervention as new ways for epilepsy treatment using the gained, detailed knowledge of circuit malfunction leading to seizure initiation and propagation. We also collaborate on a study of the complex dynamics of glioblastoma development and pathology

Research objectives:

- *Seizure genesis and propagation on single-cell and specific cell-type level*
- *Correspondence of neural circuit malfunction and specific epilepsy hallmarks*
- *Focal cortical dysplasia*
- *Epilepsy therapy*
- *Glioblastoma theranostics*

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FOCUS AND RESEARCH OBJECTIVES

Our team consists of a multidisciplinary team whose thematic focus is divided into two main directions. Structural biology group produces proteins by recombinant expression technologies and characterizes the protein or protein-ligand structures and their dynamics utilizing advanced mass spectrometric techniques. Cell signalling unit examines the linkages of cellular signalling to the metabolism of cancer cells using molecular biology and biochemistry methods. Through the collaboration of the two groups a unique research platform is formed, wherein the results obtained by the study of biological systems can also be verified and explained at the molecular level.

Research objectives:

- *Structural characterization of misfoded proteins*
- *Looking for a needle in the haystack. Detection and quantification of proteins up or down regulated in a pathology states.*

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FOCUS AND RESEARCH OBJECTIVES

We are a multidisciplinary group consisting of doctors, engineers, radiological assistants and physiologists, whose main task is to provide MRI examinations and their evaluation in the highest possible quality, meeting the latest world standards. As part of this task, we deal with implementation of new MRI protocols for routine but also non-standard brain examination for scientific purposes. In cooperation with Czech and foreign groups in the field of magnetic resonance physics, we are introducing new protocols for MRI scanning in Motol hospital, enabling an advanced examination of the patient and thus a deeper and more complex diagnosis.

Research objectives:

- *Mechanisms of ictogenesis and epileptogenesis*
- *Stroke*
- *Neuroinflammation and cerebral metabolism*
- *Neuroimaging*

SELECTED PUBLICATIONS

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FOCUS AND RESEARCH OBJECTIVE

The main clinical and research interests are 1) identification of the extent and consequences of the neurodegeneration in the adult brain with chronic drug resistant epilepsy, 2) specifying the localization of the epileptogenic area in intractable epileptic patients and 3) prediction of surgical outcome in epilepsy surgery (both resection and vagal nerve stimulation). Our group consists of neuroscientists, biomedical engineers, neuropsychologists, and technicians and for many years collaborates with scientists from Institute of Scientific Instruments of the Czech Academy of Sciences and Brno University of Technology and international centers: Mayo Clinic in Minnesota, USA and Montreal Neurological Institute and Hospital in Canada.

Research objectives:

- *Biomarkers of epilepsy*
- *Intractable epilepsy – especially mesial temporal lobe epilepsy with hippocampal sclerosis and focal cortical dysplasia*
- *Pathological and physiological brain oscillations*
- *Mechanisms of ictogenesis and epileptogenesis*
- *Role of the neurodegeneration in epilepsy*
- *Genetic (DNA-level) and transcriptomic (RNA-level) changes in focal epilepsies*

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FOCUS AND RESEARCH OBJECTIVES

We are interested in the mechanisms of interactions between neurons and oligodendrocyte lineage cells under different physiological and pathological conditions, especially in epilepsy. Recent findings have suggested that neuronal activity can regulate the number of oligodendrocyte lineage cells and their myelination activity which might have a profound feedback effect on neuronal activity and circuit function. Many pathologies of the central nervous system are accompanied by changes in myelin content in the nervous tissue, including epilepsy, where hypomyelination is usually described. Our goal is to find out how pathological neuronal activity in epilepsy affects the function of oligodendrocyte lineage cells and myelin formation.

Research objectives:

- *Neuron – oligodendrocyte precursor cells synaptic communication*
- *Myelination in epileptic tissue*
- *mTOR hyperactivity in glial cells*

SELECTED PUBLICATIONS

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FOCUS AND RESEARCH OBJECTIVE

- **Biomarkers, risk factors and modifiers of neurodegeneration with cognitive impairment**
  - **Characterize internal exposure agents and metabolites in patients with neurodegenerative disorders with cognitive impairment and identify prognostic biomarkers and exposure agent risk factors**

Numerous environmental risk factors have been proposed for neurocognitive impairment (NCI) and dementia (10.1186/s12877-016-0342-y; 10.1016/j.arr.2021.101504) and application of the exposome concept advocated to investigate Alzheimer's disease (AD) (10.1016/j.jalz.2019.06.3914) and Parkinson's disease (PD) (10.1136/OEM-2019-EPI.161).
Circulating metabolites are known to be associated with NCI and in recent years a few metabolite biomarkers for cognitive function or dementia have been validated in large-scale cohort studies (10.1016/j.jalz.2017.11.012). It is observed that many of these metabolite biomarkers are responses to exposure to chemical agents, such as pesticides (10.1038/srep32222) yet, mechanistic understanding of these disease-linked metabolites is limited (10.1073/pnas.2022857118; 10.3389/fnins.2019.00343). Greater characterization is required to identify biomarkers of environmental chemical exposures that contribute to neurodegenerative disorders. Chronic exposure to certain environmental chemicals can induce neurocognitive impairment (NCI). Analysis of circulating metabolites of patients and people presenting different degrees of cognition can enable identification of markers of chemical exposure associated with onset and progression of NCI.

Research objectives*:*

- *To identify chemical exposure agents (i.e., markers of exposure) and endogenous metabolites (i.e., markers of effect) associated to NCI and/or cognitive assessment scores.*
- *To prioritize markers representing preventable neurotoxic chemical exposure.*

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FOCUS AND RESEARCH OBJECTIVE

- **Biomarkers, risk factors and modifiers of neurodegeneration with cognitive impairment**
  - **Create a complex biomarkers signature of prodromal dementia with Lewy bodies subtype**

Lewy body diseases (LBDs) is a term describing a group of neurodegenerative disorders consisting of two major clinical entities – Parkinson's disease and dementia with LB which share many clinical and pathophysiological features. Identifying the early stages of LBDs is difficult, but very crucial for developing disease-modifying treatment since the neurodegeneration may be treated before the pathological cascades start. The main objective of this WP is the identification of subjects in the prodromal or early stages of LBD. For this purpose, we collect longitudinal data evaluating the predictive value of the core LBD features with the goal to improve diagnostics. The established core features involve Rem sleep behavior disorder, fluctuating cognition, reduced dopamine transporter uptake, and hallucinations; Apart from that, we focus on testing novel biomarkers based on magnetic resonance imaging, electroencephalography, and serum.

Research objectives:

- To collect longitudinal multimodal data from patients at risk of LBDs, patients with LBDs, AD, and HC

- To identify prodromal markers of LBDs based on quantitative data analysis.
- To train machine-learning models enabling supportive prodromal diagnosis of DLB

- **Biomarkers, risk factors and modifiers of neurodegeneration with cognitive impairment**
  - **Describe modifiable cardiovascular risk factors of cognitive decline in KardioVize population-based cohort 60+ and identify subjects at risk of degenerative dementia**

Cardiovascular (CVD) and neurodegenerative diseases (e.g. Alzheimer's disease, AD) share several common pathogenetic mechanisms and common modifiable clinical and behavioral risk factors– e.g. adiposity, high blood pressure, dyslipidemia, diabetes mellitus, smoking, physical inactivity, unhealthy diet.

The main objective of this WP is an identification of subjects in the prodromal or early stages of the two most common neurodegenerative brain diseases (Alzheimer's disease (AD), dementia with Lewy bodies (DLB) using questionnaires and scales, cognitive screening, serum AD biomarkers, acoustic speech analysis, imaging, and neurophysiological methods. Another objective is to study relationships between neurodegenerative diseases and cardiovascular and genetic risk factors.

The Kardiovize study is a longitudinal population-based evaluation of adults living in Brno and has been implemented in three phases: 1) The Kardiovize Baseline a cross-sectional evaluation of 2159 adults, aged 25-64, evaluated during 2013 – 2014; 2) The Kardiovize Parental study 65+: a cross-sectional evaluation of 274 adults, aged 65+, evaluated during 2018 – 2019; 3) The Kardiovize Follow-up: a prospective evaluation of the first group, which is an ongoing evaluation.

Research objectives:

- *To find an optimal combination of clinical and available non-invasive paraclinical examinations as suitable diagnostic markers for the early detection of patients with AD, DLB and for the evaluation of the individual risk of prodromal AD and DLB.*
- *Analysis of relationships between cardiovascular risk factors (high blood pressure, diabetes, dyslipidemia, adiposity) and biomarkers of neurodegenerative changes in the central nervous system.*

- **Neuromodulation in the treatment of cognitive impairment in neurodegeneration**
  - **Conduct an RCT targeting the cortico-hippocampal and striato-prefrontal circuits by temporal interference stimulation**

Alzheimer’s disease and its preclinical stages are characterized by progressive neurodegenerative changes in the hippocampi and default mode network resulting in dysfunctions in episodic memory and its central part the associative memory. Encoding of associative information occurs in the distributed brain networks involving inferior frontal cortex, fusiform cortex, the medial temporal lobe, premotor and posterior parietal cortex including the precuneus. Previous studies have shown that by targeting specific nodes within the cortico-hippocampal circuits via the tools of non-invasive brain stimulation the associative memory (AM) performance can be manipulated, however only relatively surface areas of this circuit were accessible by current non-invasive stimulation techniques (NIBS). Synucleinopathies, including Parkinson's disease (PD) and dementia with Lewy bodies (DLB), are neurodegenerative brain diseases characterized by an accumulation of α-synuclein in susceptible

cells within specific subcortical and cortical brain regions to form Lewy bodies and Lewy neurites. In both PD and DLB, dopamine depletion occurs in the caudate nucleus, leading to dysexecutive syndrome through disrupted association basal ganglia-thalamo-cortical circuitry. Although motor symptoms of PD can be effectively treated even at advanced stages, no causal treatment have been developed for specific non-motor symptoms such as mild cognitive impairment (MCI-PD) and PD-dementia which impact patients' independence and daily activities. NIBS techniques were shown to modulate difficult to treat PD motor symptoms and cognitive functions, however to a limited extent. Novel modalities of non-invasive transcranial electrical stimulation such as temporal interference stimulation (TIS) holds a promise to stimulate deeper brain structures without compromising the focality. TIS relies on high frequencies which can penetrate with relatively low loss. High frequency carriers (>1 kHz) emitted by two (or more) pairs of transcranial electrodes can temporally interfere at deep cortical targets. The effective stimulation frequency is equal to the offset frequency between the carriers. By controlling field orientation and frequency offset, the hot spot of constructive interference can be precisely targeted. The key aspect of this method is the use of carrier waves at frequencies higher than 1 kHz. Frequencies above this range are regarded as non-stimulating and pass-through tissues with relatively low loss. While these higher frequencies do not stimulate neural tissue, the interference envelope of two phase shifted frequencies can elicit action potentials because the offset (aka “beat”) frequency can be tuned accordingly to < 100 Hz. The latest studies showed positive behavioral effects of TIS applied over primary motor cortex or motor striatum in healthy young adults. To date, there are no studies that have investigated the effect of TIS on AM or WM.

Research objectives:

- *Conduct a blinded randomized sham-controlled cross-over trial targeting the cortico-hippocampal circuits by TIS in 20 healthy volunteers to modulate associative memory*
- *Conduct a blinded randomized sham-controlled cross-over trial targeting the caudate by TIS in 20 volunteers with MCI to modulate working memory*
- *Use fMRI/EEG-TMS recordings concurrently-with/before-after TIS and relate them to TIS-induced behavioural performance changes in both trials.*

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FOCUS AND RESEARCH OBJECTIVES

The group is focused on analysis of speech and language disorders in neurodegenerative disorders. We aim to integrate speech assessment into clinical practice as a viable biomarker of neurodegeneration for early diagnosis and monitoring treatment efficacy and disease progression in movement disorders.

Research objectives:

- *To harmonize research protocols and provide the methodology for speech assessment at the country level.*
- *To describe severity and patterns of speech disorder across various neurodegenerative disorders and relate them to other clinical markers of neurodegeneration.*
- *To investigate distinct motor speech markers across disease type, dysarthria type, and dysarthria severity for potential differential diagnosis.*
- *To explore the sensitivity of linguistic markers to detect cognitive deterioration due to neurodegeneration.*
- *To evaluate the feasibility of remote speech screening for the detection of neurodegeneration.*
- *To evaluate the effect of normal ageing on speech in large sample of healthy subjects.*
- *To explore effects of therapy on speech performance in neurodegeneration.*

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FOCUS AND RESEARCH OBJECTIVES

Development of methods for remote monitoring, rehabilitation and training of motor and cognitive functions.

Remote rehabilitation focuses on improving functionality in neurological patients without physical interaction with a therapist using modern technologies such as mobile applications, virtual reality, teleconferencing and others. The present research objectives are to develop and test methods to improve functionality and mobility of patients with neurological disorders affecting motor and cognitive functions. Namely, it concerns devices, mobile apps and computer programs that allow patients to exercise and interact with a therapist remotely and to receive sensory and motor feedback to help patients mimic and perform movement correctly.

Research objectives

- *test the feasibility of a commercial Activity Tracker device for multi-day monitoring of gait, heart rate and other monitored functions in patients with Parkinson's disease (PD)*
- *develop protocol and test efficacy of expiratory muscle strength training (EMST) using a mobile phone-based visual feedback (MPVF) app in patients with Parkinson disease, and multiple system atrophy*
- *test the effect of remote and group-based cognitive rehabilitation on gait and cognitive function in Parkinson disease*

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FOCUS AND RESEARCH OBJECTIVES

Research Unit for Rare Diseases (RURD) is a part of the Department of Paediatrics and Inherited Metabolic Disorders of the First Faculty of Medicine and BIOCEV. RURD research program aims at understanding the causes of the whole range of rare human diseases and roles of rare genetic variants in pathogenesis of complex diseases. In close collaboration with clinician-researchers, RURD projects utilize complex clinical, biochemical, and molecular genetic information gathered from unique cohorts of patients with diseases/phenotypes of interest. Biological samples from the patients are tested in parallel. RURD studies integrate a wide range of genomic, bioinformatic, molecular genetic, biochemical and cell biological/pathological methodologies.
RURD is a key member laboratory of the National Center for Medical Genomics (NCMG, www.ncmg.cz). NCMG is a national research infrastructure that secures integrative instrumental, methodological and experimental expertise for genome sequencing, transcriptome and epigenome analyses, cytogenomic studies and whole genome genotyping. Computational, data storage/processing capacity and bioinformatic/statistical support is also provided by NCMG.
Within NINR, RURD provides an infrastructure for identification and (functional) characterization of genetic variants causing selected rare or complex neurological diseases.

Research Objectives

- *To provide instrumental (sequencing), computational and bioinformatic/statistical platforms for analyses of the human genome to other collaborating NINR research groups.*
- *We aim to establish the diagnosis(es) and understand the etiology of selected neurological diseases and/or defined neurological phenotypes in collaboration with clinical researchers participating on the project. We will focus our studies on patients (and their families) with*

neurometabolic diseases, adult forms of neuronal ceroid lipofuscinosis, Wilson disease, and familial dystonia. We will also evaluate patients with severe neurological or neuropsychiatric affliction with unknown (but genetically suspect) origin.

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FOCUS AND RESEARCH OBJECTIVES

Our laboratory is dedicated to advancing the understanding of prenatal development, with a specific research focus on neuroplacentology and the intricate interplay of the placenta-brain axis. With expertise spanning placental biology, genetics, biochemistry, physiology, and clinical research, our team aims to decipher the impact of maternal-fetal interactions on fetal brain development and programming. A pivotal aspect of our investigations revolves around comprehending the multifaceted roles of the placenta, including hormone and neurotransmitter production and degradation. Recent evidence has illuminated the developmental origins of various adult brain disorders, highlighting the pivotal role of in utero neurotransmitter signaling in shaping optimal fetal brain wiring. Building upon this foundation, our research in the past three years has centered on unraveling the delicate equilibrium of monoamine homeostasis within the fetoplacental unit. Notably, our team was the first to identify a novel placental monoamine uptake by the organic cation transporter 3, shedding light on the intricate mechanisms governing fetal brain development. We aim to continue to broaden our understanding of the placenta-brain axis and its significance in shaping lifelong neurological outcomes.

Research objectives:

- *Effects of endocrine disruptors (EDs) on the placenta-brain axis and fetal neurodevelopment.*
- *Effects of maternal obesity (induced by high-fat diet) and maternal immune activation (induced by LPS) on mTOR signaling in the rat placenta and fetal brain.*

- *mTOR signaling in placentas obtained from pathological pregnancies*

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FOCUS AND RESEARCH OBJECTIVES

- **Biomarkers, risk factors and modifiers of neurodegeneration with cognitive impairment**
  - **Develop and cross-validate translational diagnostic tests aimed at spatial memory**

There is a growing worldwide effort to find novel simple, reliable and cost-effective markers being able to detect and monitor subtle cognitive changes in very early Alzheimer's disease (AD) because the treatment influencing AD pathological processes is most effective in the early clinical stages. Spatial navigation is a cognitive process that relies on brain regions that are first affected by AD pathology. Therefore, spatial navigation impairment is a very promising early marker of AD. The advantage of using spatial navigation as a measure of cognitive performance is that it can be tested using similar paradigms in humans and rodents and thus offers a unique opportunity for translational research which would be useful for both the clinical diagnosis and research of new potential therapies.

Research objectives

- *to establish cognitive translational research in AD*

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FOCUS AND RESEARCH OBJECTIVES

- **Biomarkers, risk factors and modifiers of neurodegeneration with cognitive impairment**
  - **Investigate age-related structural changes in neurons of the hippocampus and central auditory system in animal models of dementia**

This work package is focused on studying mutual relationship between deficits in central part of auditory system and cognition (particularly spatial and social cognition) in rodent models of Alzheimer's disease (AD). To this aim, a rat model of AD on Fischer 344 (F344) background will be used. The rat strain Fischer 344 (F344) offers a unique approach for studying pathological processes behind dementia and presbycusis. F344 rats develop relatively soon age-related hearing loss with a fast progression. In addition, a transgenic rat model of AD (TgF344-AD) is available as a model of progressive deteriorating cognition. These rats have incorporated a human mutant gene for amyloid precursor protein (APP) and a human gene for PSEN1 lacking exon E9. Furthermore, to get more translationally powerful and valid results, we will perform the same experiments with analogous mice AD model (B6;C3- Tg(APPswe,PSEN1dE9)85Dbo/Mmjax) carrying the same human AD-related genes.

Research objectives:

- *Characterize with the aid of quantitative morphometry changes occurring with aging in the structure of neurons in the inferior colliculus (IC), medial geniculate body (MGB), auditory cortex (AC), and hippocampus (HC).*

Hypothesis: Accelerated age-related reduction in neuronal arborization in AD animals will take place both in auditory structures and the hippocampus. Description: Detailed changes in the morphology of neurons in the auditory structures (inferior colliculus, IC; medial geniculate body, MGB; auditory cortex, AC) and cognition-related structures (hippocampus, HC) induced by aging in wild-type and transgene will be studied using the Golgi-Cox staining technique. A random sample of the region-specific type of neurons will be traced and evaluated using Neurolucida software (MBF Bioscience). This allows us an advanced neuronal morphology analysis, including measuring the length and volume of neuronal dendrites, number of dendritic branches, their complexity, number of synaptic spines, and Sholl analysis. In addition, we plan to estimate the number of neurons in the mentioned brain structures in TgF344-AD and the WT using StereoInvestigator software (MBF Bioscience).

- *Compare age-related changes in the function of the auditory system based on the measurement of thresholds of auditory brainstem responses (ABR) and distortion-product otoacoustic emissions (DPOAE).*

Hypothesis: AD animals will exhibit earlier onset of the auditory threshold increase and a deficit in DPOAE Description: In contrast to available detailed information about the function of the auditory system in Fischer 344 rats, there is no comprehensive information on the auditory function in TgF344-AD rats. We plan to measure hearing thresholds in all animals by recording auditory brainstem responses (ABR) and distortion-product oto-acoustic emissions (DPOAE) under isoflurane anesthesia. The function of the auditory system will be also evaluated using prepulse inhibition of (acoustic) startle reflex as this measure has been found to be impaired at early stages in other AD models.

- *Compare age-related changes in the cognitive function as measured by spatial memory tests and social cognition tasks.*

Hypothesis: AD animals will display deficits in both spatial memory and social cognition.
Description: Spatial memory will be assessed in a standard Morris water maze in which animals must search for an underwater platform to escape from water. Social behavior will be evaluated in a social interaction task, in which social interactions (contacts, sniffing) with an unknown conspecific are recorded in freely moving animals in the open-field. Furthermore, a Five-Trial Social Memory Test will allow us to find out if an animal can differentiate between a repeatedly presented intruder animal and another novel intruder animal, thus expressing working social memory.

- *Compare electrophysiological signatures such as local field potentials in the hippocampus while performing social cognition tasks.*

Hypothesis: AD animals will show disturbances in the local field potentials (LFP), particularly in the gamma and theta range. Description: For the Five-Trial Social Memory test, both AD mice and rats will be implanted with electrodes over dorsal hippocampal areas CA1 or CA2 and their LFPs will be recorded to evaluate the effect of AD on social memory-related brain oscillations.

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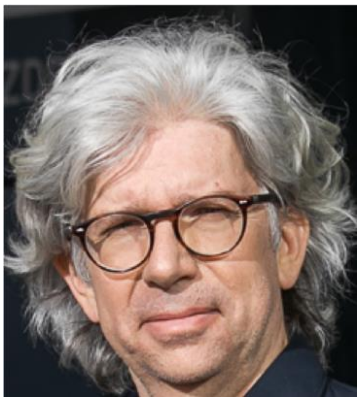

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FOCUS AND RESEARCH OBJECTIVES

- **Impact of COVID-19 on brain functions: Central mechanisms of post-COVID syndrome**
  - **The central mechanisms of long-covid syndrome from the subcellular to the macrostructural (MRI) level**

In order to track brain insult as a sequelae of SARS-CoV-2 infection, we aim to combine pre/post-COVID high-dimensional data of different modalities including structural magnetic resonance imaging (sMRI), circulation protein biomarkers sensitive to disruption of different cellular CNS compartments along, with sensitive miRNA biochip. Combination of those approaches might represent a leap forward in unveiling the central effect of SARS-CoV-2. The aim of this proposal is to get insight into the complex association patterns among these heterogeneous and complementary data that might be of substantial benefit to the unraveling of the cellular damage caused by SARS-CoV-2 neurotrophic effect and combined clinical sequelae with disruption of the brain clearance system.

The strength of our proposal lies in the existence of a large-scale pre-COVID MRI database and blood samples storage form healthy subjects (HSs) previously participating in NIMH-organized research. A proportion of HSs were, in the meanwhile, confirmed as COVID-19 PCR-positive (COVID+).This allows us to perform an unique pre/post COVID study with use of MRI morphometry and multiplex biomarker approach. We intend to perform within-subject pre/post COVID examinations in n=80 COVID+ subjects along with n=80 COVID-negative HSs with two MRI+blood sampling. To our knowledge this would represent the first thorough longitudinal assessment of brain changes caused by SARS-CoV-2.

Research objectives

- *We aim assess the function of glymphatic brain clearance system as assessed by means of MRI in a pre/post Covid manner*
- *We will perform biomarker profiling before and after SARS-CoV-2 infection (miRNA, S100B, NSE, NF-L, GFAP, UCH-L1) as the multimodal substrate of the long-COVID syndrome.*
- *We will focus on the link between the glial-lymphatic brain waste clearance system and subcellular markers of cellular injury as a unifying factor behind long-term sequelae of SARS-CoV-2 neuroinfection.*

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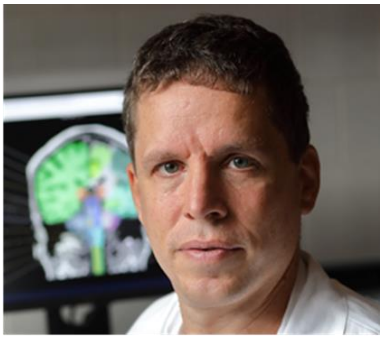
Vyhnálek Martin



NODE

Prague

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FOCUS AND RESEARCH OBJECTIVES

Centre of Hereditary Ataxias based in Motol University Hospital in Prague, member of the European Network for Rare Diseases ERN-RND, is a reference center providing diagnostic and therapeutic care for patients with hereditary cerebellar diseases. The center is involved in the registers and initiatives EFACTS (European Friedreich's Ataxia Consortium for Translational Studies) and AGI (Ataxia Global Initiative), which aim to monitor natural disease development and search for biomarkers, thus preparing the groundwork for research of new treatment.

Research objectives:
Using advanced gene testing methods (including clinical exome analysis, in reasonable cases whole exome/genome sequencing) and neurophysiological, neuropsychological, and biochemical methods the project aims to:

- *Uncover and describe rare genetic causes of ataxias, including the description of novel mutations.*
- *Examine and describe the spatial navigation impairment and other cognitive and neuropsychiatric features in patients with cerebellar ataxias and in an animal model of SCA 1 mice.*
- *Describe the cognitive, functional, and biochemical changes (incl. functional testing, oculomotor digital biomarkers, bio sampling etc.) in SCA and Friedreich's ataxia.*

- **Biomarkers, risk factors and modifiers of neurodegeneration with cognitive impairment**
  - **Define early neuropsychological markers of physiological and pathological aging**

Activities according to the three goals (challenging cognitive tests; subjective cognitive complaints; neuropsychiatric symptoms):
According to the plan, we have built on the established framework of the CBAS associated with Motol University Hospital (www.cbas.cz). We have consolidated the retrospective cross-sectional data from the REDCap in-house database and optimized the standard and experimental neuropsychological and questionnaire protocol for data collection. Since the beginning of the project, we examined 189 participants and administered the whole optimized protocol to them (individuals with subjective cognitive decline, mild cognitive impairment, and cognitively normal controls). Recruitment of participants continues. We combined the newly collected data with those collected earlier within the CBAS study and initiated the data analysis. The content and direction of the investigations are reflected in the working titles of the planned manuscripts (see below).

Research objectives:

- *Mild behavioral impairment in early Alzheimer´s disease and its association with APOE and BDNF risk genetic polymorphisms (under peer review in Alzheimer´s Research and Therapy)*
- *Differential Cued Recall Memory Impairment in Mild Cognitive Impairment due to Alzheimer's disease versus Parkinson's Disease*
- *The role of confabulations in the challenging Memory Binding Test for early Alzheimer´s disease diagnosis*
- *Specific memory binding indexes and their potential to discriminate between Alzheimer´s disease biomarker-positive and biomarker-negative older adults*

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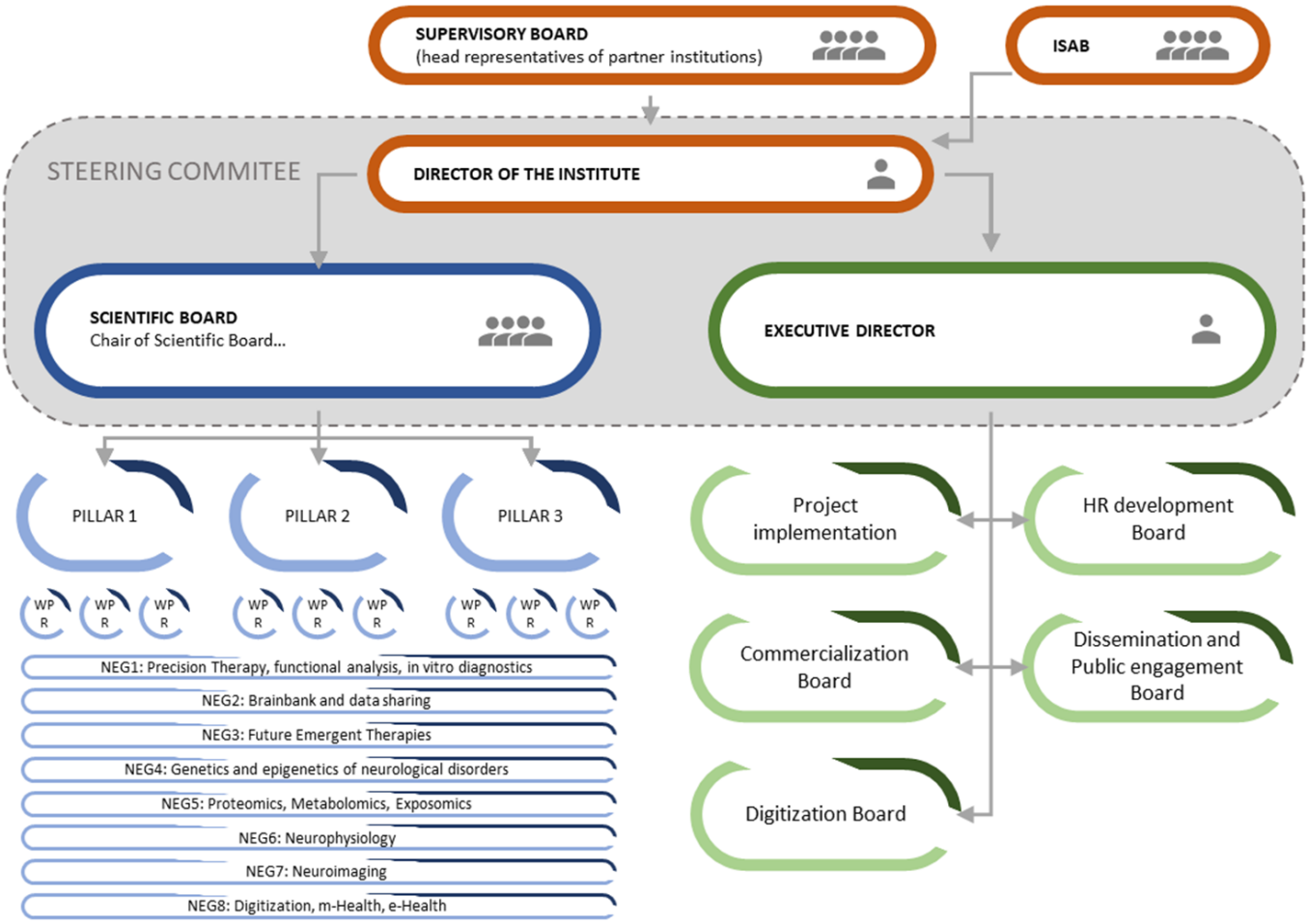

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