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Abstract Book

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Neuropitches

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P25 - Anke Claessens (Peripheral Neuropathy Research Group): Targeting axonal transport defects in Charcot-Marie-Tooth disease type 2J

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P29 - Isa Decuypere (Laboratory of Cell Biology and Histology): Defining the role of nuclear envelope stress in glioblastoma

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P31 - Melanie Van Brussel (Peripheral Neuropathy Research Group): Development of a 2D Co-Culture System to Uncover Schwann Cell-Macrophage Interactions in CMT1A

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P66 - Mathijs van der Lei (MEDGEN): Screen to Cure: SCREEN4PN & MouseKing

Mapping the cell state plasticity of patient-derived glioma stem-like cells

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Glioblastoma is the predominant form of brain cancer in adults. Due to its aggressive nature, less than 10% of patients survive longer than 5 years post-diagnosis. To date, no treatment is available that can eradicate all tumor cells and avoid relapse. This is in part due to the presence of stem-like glioma cells (GSCs), which can self-renew, invade and communicate with each other and the tumor microenvironment. Recent single cell transcriptomics analyses have revealed a continuum of four distinct transcriptional signatures within the GSC population. However, significant cell state plasticity within and between patients complicates our understanding of their individual contribution to GBM aggressiveness. To address this gap, we are developing an microscopy strategy to map individual cell states in relation to the local tumor microenvironment. First, we have established and validated a multiplex marker panel that allows unequivocal documentation of the four major cell states. Using this panel, we found significant heterogeneity in cell state composition in a panel of patient-derived GSCs. When growing the GSCs as 3D tumoroids, we could observe a phenotypic switch over time which differs between patients. Next, to fully recapitulate the different zones of the tumor microenvironment, we established an assembloid model by fusing a cerebral organoid with a GSC-derived tumoroid. Using an-house developed pipeline for in-flow, high-throughput light-sheet microscopy, we are currently screening assembloids with different patient cells to correlate GSC subtype diversity with infiltrative behavior. This will allow us to untangle the connection between GSC plasticity and tumor aggressiveness. Stratifying patient- and cell-specific migration patterns will offer an unprecedented view on in situ GSC behavior and pave the way to more personalized treatment in the future

Evaluating structural alterations and neuroinflammation in a non-human primate model of Batten Disease

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Batten disease (BD) is a rare, fatal pediatric neurodegenerative disease, characterized by progressive intellectual and neurological degradation. A defining feature of BD is a lysosomal storage dysfunction in the neuronal cytoplasm. This dysfunction causes the accumulation of waste material called ceroid lipofuscin in lysosomes, leading to cell dysfunction and death. The main cause of this defect lies within a genetic recessively inherited mutation of the neuronal ceroid lipofuscinoses (NCL) genes. BD is an umbrella term covering different NCL mutation types, ranging from CLN1 to CLN14. Common symptoms across subtypes include visual deficits, seizures, motor deficits, and dementia. Currently, there is no cure for BD and diagnosis in humans remains challenging due to the rarity of the disease and lack of biomarkers. The Oregon National Primate Research Center (ONPRC) found the spontaneous emergence of a CLN7-\- mutation in their non-human primate (NHP) Japanese macaque colony that recapitulates the CLN7-\- mutation observed in humans.

By using different imaging modalities, this research aims to investigate how the CLN7-\- mutation affects the brain of the macaques and to identify suitable translational imaging biomarkers. Specifically, we use magnetic resonance imaging (MRI) to assess structural brain changes and positron emission tomography (PET) imaging to measure glucose metabolism ([18F]FDG PET) and neuroinflammation ([11C]PBR28 PET). Since macaques share many similarities with humans in brain structure, development and function, this model could help in development of future therapies for this devastating childhood disease.

Establishing normative data for the assessment of the Subjective Postural Vertical using a motorized tilting chair

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Estimating the orientation of objects or the body relative to gravity is an automatic process in humans. For example, you can instantly recognize when a painting is slightly tilted, that the Tower of Pisa is leaning instead of standing perfectly upright, or that you are standing tilted on a sloped street. However, after a stroke, the ability to perceive verticality can be impaired. Verticality perception refers to the ability to estimate the true vertical position, parallel to the gravitational vector, which is considered 0°. When you have difficulties with accurately estimating the vertical, this could hamper the stroke patient during daily life activities.

During my PhD project, I focus on estimating verticality perception in stroke patients. In this study, we focus on the Subjective Postural Vertical: this measurement can be used to measure an individual's internal sense of body orientation relative to the gravitational vector. When estimating the accuracy of verticality perception, you can measure the deviation from the true vertical in degrees, and also the variability in estimations. In stroke patients, we often see that they are insecure about the vertical position, and therefore are highly variable in their esimations (for example, estimation trial 1 -9° and trial 2 +5° deviation from the true vertical). To differentiate between normal accuracy and abnormal, we evaluated 60 healthy participants.

To examine the SPV, the participant is sitting in a motorized tilting chair which can tilt sideways. The participant can use a remote control to bring the chair from a tilted position, to the perceived neutral position. The examiner uses an inclinometer to see how many degrees the perceived vertical position is tilted from the true vertical position.

With this study, we want to share our insights about normative data of the Subjective Postural Vertial gathered without new developed tilting chair.

Same gene, different outcomes: Insights into the expanding landscape of RNA polymerase III disorders

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RNA polymerase III (Pol III) is a large enzymatic complex responsible for transcribing small noncoding RNAs. Pathogenic variants in multiple genes encoding Pol III subunits are known to cause neurological disorders such as hypomyelinating leukodystrophy (HLD), Wiedemann-Rautenstrauch syndrome (WRS), and spastic ataxia/paraplegia. These disorders, collectively known as POLR3-related disorders, primarily affect the central nervous system (CNS) and are caused by biallelic mutations to Pol III subunit genes.

Our group recently identified a patient with a de novo variant in the POLR3A gene encoding the largest Pol III subunit. The proband presented with early-onset, severe demyelinating Charcot-Marie-Tooth (CMT) disease which is a disorder of the peripheral nervous system (PNS). Through international collaboration, we identified ten additional patients from seven distinct families worldwide, all carrying monoallelic POLR3A variants linked to similar CMT-like clinical features. Notably, these patients do not show the cardinal CNS features typical for patients with biallelic POLR3-related disorders. Our functional genomics studies suggest that these newly identified POLR3A variants disrupt the Pol III complex assembly and cause downregulation of crucial RNA molecules transcribed by Pol III. Interestingly, the CMT-causing variants occur in close proximity to those causing biallelic POLR3-related disorders, yet they result in a distinct phenotype affecting the PNS rather than the CNS.

This discovery expands the clinical landscape of POLR3-related disorders beyond classical CNS phenotypes and underscores the importance of considering monoallelic POLR3A variants in the genetic evaluation of peripheral neuropathies, thus improving the diagnostic yield.

Endocannabinoid Neuroenzyme PET Imaging in Huntington's Disease mice

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Huntington's disease (HD) is an autosomal dominant, progressive, neurodegenerative disorder characterized by CAG triplet repeat expansion in the Huntingtin (HTT) gene. This genetic mutation causes the formation and aggregation of the mutant Huntingtin protein, leading to neurotoxicity. Clinically, HD is characterized by movement disorders, dementia, and behavioral and psychiatric manifestations. No effective treatment for HD has been demonstrated to date. Once people with HD receive their diagnosis, there is little hope. Research on new diagnostic and therapeutic targets is essential to better understand the mechanisms of HD. Current work specifically focuses on the endocannabinoid α/β-Hydrolase Domain 6 (ABHD6). The role of ABHD6 in HD pathogenesis remains unclear, however its inhibition has been shown to improve motor coordination symptoms in a HD mouse model. Our research aims to further investigate changes in ABHD6 levels in the zQ175DN mouse model of HD using the ABHD6-targeting radiotracer [18F]JZP-MA-11 for positron emission tomography (PET), a non-invasive in vivo imaging technique. Specifically, we set three key objectives. Objective (1) is the implementation of the novel [18F]JZP-MA-11 radiotracer at our radiopharmacy department. Objective (2) is to determine the optimal kinetic modeling approach for [18F]JZP-MA-11 and to validate the ability of [18F]JZP-MA-11 PET to detect ABHD6 levels in wild-type mice. Lastly, objective (3) focuses on in vivo [18F]JZP-MA-11 PET in heterozygous zQ175DN mice and wild-type littermates to assess ABHD6 levels in the brain, more specifically in the striatum, motor cortex, hippocampus, thalamus and cerebellum. Several timepoints will be investigated (age 3, 6, 9, and 12 months). By exploring ABHD6 in HD, we strive to make meaningful steps in HD research and offer hope to patients and their families.

Neuromuscular models to investigate Charcot-Marie-Tooth disease

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Charcot-Marie-Tooth (CMT) disease is the most common hereditary peripheral neuropathy, leading to symptoms ranging from muscle weakness to sensory loss. While numerous animal models have been developed, their limited success in translating to therapies highlights the need for new disease models derived from human cells. In recent years, several in vitro human stem cell-based models have been developed to investigate the peripheral nervous system. Most of these models are 2D monocultures of motor neurons, which are straightforward to analyze and can mimic some CMT features. Unfortunately, these models are insufficient for studying the complex 3D myelination process, which involves both motor neurons and supporting Schwann cells, as well as crucial neuron-muscle interactions, processes that are disrupted in patients with CMT.

Therefore, within the Peripheral Neuropathy Research group, we are creating various advanced neuromuscular models. On one hand, we are optimizing neuromuscular organoids and assembloids, which are two different 3D stem cell models consisting of multiple cell types. Although, these 3D models are able to mimic important peripheral nerve hallmarks, such as myelination and neuron-muscle interactions, these models are difficult to scale up for high-throughput use. On the other hand, we are developing microfluidic models that will enable easier readouts but currently lack myelinating Schwann cells.

In summary, while we do not yet have a single model that can investigate all CMT hallmarks, we are moving towards the creation of multiple models, each with its own specific application and end goal. The potential value of these models goes beyond CMT and can also be translated to other peripheral nerve diseases.

A Data-driven Approach to Microstructural Imaging (ADAMI)

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The ability to study tissue microstructure in vivo and completely noninvasively using magnetic resonance imaging (MRI) has the potential to radically change how we detect, monitor, and treat diseases, in particular the many neurodegenerative diseases that affect our world's aging population. Unfortunately, MRI provides a very indirect measure of microstructure, and a variety of contributing factors complicates one-to-one association between the MRI measurements and the microscopic substrate. As a result, microstructural mapping is still a poorly understood and challenging inverse problem that often yields inconsistent and contradictory outcomes.

Funded by the European Research Council, the ADAMI project is shifting from the traditional model-driven approach to a data-driven methodology. Rather than relying on a single source of contrast, we exploit the versatility of MRI and use multiple, independent contrast mechanisms that provide the necessary information to distinguish reliably between microscopic substrates. Rather than relying on preconceived models and slow and unreliable model fitting routines, we use machine/deep learning to learn appropriate models and efficient and robust fitting routines directly from the data. Rather than performing a posteriori histological validation of these new microstructural models, we will acquire a priori histological data to directly inform this learning process, guaranteeing, for the first time, a close match between microstructural readouts obtained from MRI and invasive histology.

Through these innovations, ADAMI will advance the field of medical imaging by introducing a groundbreaking data-driven approach to microstructure imaging which will significantly impact the understanding, diagnosis, and monitoring of brain diseases and beyond.

The road towards implementation of TMEM106B genetic testing in clinical practice in progranulin pathogenic variant carriers

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Clinical genetic testing has been focused on autosomal dominant risk-increasing mutations rather than on genetic modifiers of disease. While TMEM106B has been shown to modify disease penetrance in GRN pathogenic variant carriers, genotyping of TMEM106B in GRN pathogenic variant carriers is currently not conducted in a clinical setting, not even in the event of a positive genetic test result for GRN in an asymptomatic individual.

Through characterization of the TMEM106B haplotype in large well-characterized cohorts of GRN pathogenic variant carriers, we aim to provide support for implementation of TMEM106B genetic testing in GRN pathogenic variant carriers in clinical testing.

Systematic genotype screens for TMEM106B haplotype in well-characterized cohorts are conducted.

Our preliminary data indicate a lower proportion of individuals homozygous for the protective TMEM106B haplotype in GRN carriers compared to individuals with a C9orf72 repeat expansion, MAPT pathogenic variant or non-mutation carriers. The majority of GRN carriers homozygous for the protective TMEM106B haplotype are asymptomatic. Importantly, some are still healthy despite relatively old age (> 70y). In those that are symptomatic, we have identified a case with a CSF1R mutation on top of the GRN mutation with a Parkinson-like phenotype. Whole genome sequencing is currently ongoing to further investigate other genetic causes of disease in symptomatic GRN carriers homozygous for the protective TMEM106B haplotype.

Through investigation of TMEM106B haplotypes in GRN carriers we show that individuals with a GRN variant and homozygous for the protective haplotype are still healthy despite relatively old age, and that the disease in those affected might be caused by other genetic factors. Screening for TMEM106B in a clinical setting has important implications for genetic counselling and clinical trial inclusion criteria for GRN carriers.

A performance validation of six commercial wrist-worn wearable devices for sleep stage scoring compared to polysomnography

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Study Objectives: Wearable devices for sleep tracking have gained immense popularity over the past few years. The aim of this study is to assess the performance of six different consumer wearable devices, namely the Fitbit Charge 5, Fitbit Sense, Withings Scanwatch, Garmin Vivosmart 4, Whoop 4.0 and the Apple Watch Series 8, for detecting sleep parameters compared to the gold standard, polysomnography (PSG).

Methods: Sixty-two adults (52 male, 10 female, mean age ± SD = 46,0 ± 12.6 years) spent a single night in the sleep laboratory with PSG while simultaneously using two to four wearable devices.

Results: The results indicate that most wearables displayed significant differences with PSG for total sleep time (TST), sleep efficiency (SE), wake after sleep onset (WASO) and light sleep (LS). Nevertheless, all wearables demonstrated a higher percentage of correctly identified epochs for deep sleep (DS) and REM sleep compared to wake (W) and LS. All devices detected >90 % of sleep epochs (i.e., sensitivity), but showed lower specificity (29.39 % to 52.15 %). The Cohens Kappa coefficients of the wearable devices ranged from 0.21 to 0.53, indicating fair to moderate agreement with PSG.

Conclusions: Our results indicate that all devices can benefit from further improvement for multi-state categorization. However, the devices with higher Cohens Kappa coefficients, such as the Fitbit Sense (κ = 0.42), Fitbit Charge 5 (κ = 0.41) and Apple Watch Series 8 (κ = 0.53), could be effectively used to track prolonged and significant changes in sleep architecture.

Exploring Dopaminergic Pathways in the Brain Using Preclinical Pharmacological MRI

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Disruptions in neurotransmitter systems, including the dopaminergic system, occur in various neurological and neuropsychiatric disorders such as schizophrenia, addiction, and Parkinson's disease. Understanding how dopamine pathways function in the healthy brain and how they are altered in disease is essential for developing effective treatments.

In this project, we aim to establish a novel preclinical pharmacological MRI (phMRI) protocol to study the two main dopaminergic pathways: the direct and indirect pathways. phMRI represents a powerful non-invasive method that combines functional MRI with a pharmacological compound to study how the brain responds to the modulation of specific pathways. By analyzing changes in brain activity following the administration of drugs that selectively affect dopamine receptors in the direct and indirect pathways, we aim to map pathway-specific responses across the brain.

Using a 9.4T MRI system, we acquired whole-brain phMRI data (5 s/image, resolution = 0.3 mm) from anesthetized mice. Ten minutes prior to scanning, domperidone (intraperitoneal, i.p.) was given to minimize peripheral effects of the pharmacological compounds. After 15 min. of baseline scans, a drug mixture of either D1-receptor agonist and D2-receptor antagonist (to interrogate the direct pathway) or D2-receptor agonist and D1-receptor antagonist (to interrogate the indirect pathway) was injected as a bolus via an i.p. infusion line. The acquisition continued for an additional 51 min. to allow investigation of temporal pathway-specific changes.

PhMRI data are processed using Matlab R2021a and SPM12 and analyzed with a focus on key dopaminergic brain regions such as the caudate putamen, globus pallidus, and motor cortex.

Our goal is to apply this method first in healthy subjects and later in animal models for dopaminergic disorders to enhance our understanding of alterations in dopaminergic signaling and to guide the development of novel and effective therapies.

Gaze control during walking: a gateway to understanding sensory and cognitive functioning, dynamic postural control, and fall risk in older adults?

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Gaze control – the ability to perceive and follow (moving) objects effectively - is crucial for safe mobility, yet its role in fall risk among older adults remains largely overlooked. Navigating real-world environments requires individuals to efficiently control their gaze in order to perceive, predict, and track moving objects—abilities that depend on the coordination of sensory, cognitive, and motor processes. Impaired gaze control may therefore reflect broader declines in these functions, making it a valuable proxy for fall risk.

Current fall prediction models, based on controlled laboratory tasks, often lack ecological validity. They typically assess sensory, cognitive, and motor deficits in isolation, neglecting their integration during real-world navigation and overlooking the role of gaze control. However, gaze control is linked to established fall risk factors, such as sensory and cognitive impairment, and postural instability, yet remains underexplored as a neurobiological marker of fall risk.

This study proposes that gaze control could serve as a key predictor of fall risk, as it may potentially reflect underlying deficits in sensory, cognitive, and motor functioning. It also hypothesizes that integrating gaze control into fall prediction models will significantly enhance their accuracy.

To address previous methodological limitations, this research employs Augmented Reality to create dynamic, life-like environments while simultaneously tracking gaze. This innovative approach provides a more ecologically valid and comprehensive framework for assessing fall risk, bridging the gap between controlled experiments and real-world navigation

High epilepsy prevalence and excess mortality in onchocerciasis-endemic counties of South Sudan: A call for integrated interventions

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Background: Epilepsy poses a significant public health burden in onchocerciasis-endemic regions with intense transmission. This study examined epilepsy prevalence, mortality and the association between onchocerciasis transmission and epilepsy, including probable nodding syndrome (pNS), in five counties of South Sudan.

Methods: House-to-house cross-sectional surveys (2021–2024) identified suspected persons with epilepsy (sPWE) and retrospectively documented mortality among sPWE and individuals without epilepsy (IWE). Epilepsy diagnoses, including pNS, were confirmed by trained clinicians. Ongoing transmission was assessed using anti-Ov16 seroprevalence in children aged 3–9 years. Age- and sex-standardised prevalence rates, mortality rates and standardised mortality ratios (SMRs) were calculated with 95% confidence intervals (95%CIs), using IWE as the reference population. The association between epilepsy and anti-Ov16 prevalence was explored using weighted arcsin-transformed linear regression.

Results: Among 34,345 individuals screened, epilepsy prevalence was 4.1% (range: 2.3–7.1%), and pNS prevalence was 1.5% (range: 0.6–2.2%). Anti-Ov16 seroprevalence among children was 23.3% (range: 1.4–44.1%). Each 1.0% increase in anti-Ov16 seroprevalence was associated with a 0.10 percentage point rise in epilepsy prevalence and a 0.04 percentage point rise in pNS prevalence. Median age at death was lower for sPWE (20 years) than for IWE (39 years; $p<0.0001$). Mortality rates per 1,000 person-years were significantly higher in sPWE (48.4, 95%CI=41.9-55.8) than in IWE (6.1, 95%CI=5.6-6.7). The overall SMR was 6.8 (95%CI=5.8-7.8), indicating sPWE were seven times more likely to die than IWE.

Conclusion: The high epilepsy burden in onchocerciasis-endemic areas is characterised by increased prevalence and mortality. Strengthening integrated onchocerciasis and epilepsy programmes is crucial to reducing epilepsy incidence and ensuring continuous access to antiseizure medication.

Vulnerability and resilience for mental illness following viral infections in the NESDA deep-phenotyped longitudinal cohort

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Infectious diseases significantly elevate the risk of developing mental illness (MI), with an estimated 30% of the population exhibiting vulnerability for post-infection MI. Despite previous research efforts, underlying pathophysiological mechanisms driving this relation remain unidentified. It is hypothesized that infections can trigger neurobiological changes in the central nervous system, leading to psychiatric symptomatology. To understand these mechanisms, fine-grained clinical and biological data are required, which are immensely difficult to obtain.

In this state-of-the-art study, we will investigate the impact of SARS-CoV-2 seroconversion on the relapse risk of MI and its underlying mechanisms. Our investigation uses a unique, large-scale, longitudinal deep-phenotyped database including biomarkers, genome-wide association study (GWAS), neuroimaging, and psychosocial data. We have collected blood samples and clinical data before and after the COVID-19 pandemic in individuals vulnerable for depressive and anxiety disorders. We hypothesize that infections increase the risk of MI relapse in vulnerable individuals.

MI imposes a major personal, societal, and economic burden worldwide. However, clinical guidelines for identifying, managing or preventing infection-related mental health complications are lacking. By advancing our understanding of the pathophysiology of post-infection MI, our research can facilitate the development of novel personalized therapeutic and preventive strategies.

Structural and Resting-State Effective Connectivity in a Non-Human primate Model of Huntington's Disease

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Huntington's disease (HD) is a genetic neurodegenerative disorder caused by expanded CAG repeats in the huntingtin (HTT) gene leading to striatal atrophy that progresses to the cortex and white matter and results in motor dysfunction and cognitive decline. Recently, a non-human primate (NHP) model of HD was developed via injection of an adeno-associated viral vector expressing 85 CAG repeats into the striatum. This model captures several neuropathological changes and symptoms observed in people with HD (PwHD) including chorea and mild cognitive impairment. A longitudinal investigation using multimodal MRI in this model revealed volumetric and resting-state functional connectivity (rs-FC) changes in comparisons with a controls group, in key regions involved in HD over the course of 30 months post the virus injection.

We aimed to study longitudinal changes from baseline across 5 timepoints (3, 6, 9, 14, and 20 months) in structural connectivity (SC), obtained from the diffusion MRI (dMRI) scans acquired in the model primates (n=6, 4 males, 2 females) vis-à-vis the buffer group (n=5, 4 males, 1 female). Additionally, going beyond the correlative FC analyses, we aimed to analyse changes in causal, inter-regional interactions by estimating effective connectivity (EC) in each animal, from its rs-functional MRI scan, constrained to strong structural connections.

SC between basal ganglia regions and the cortex in the HTT85Q group – key regions involved in HD, was significantly reduced compared to the buffer group, at 14 months post-surgery. EC from the caudate and putamen to the motor cortex regions was reduced at 3-months post-surgery.

SC between basal ganglia regions and the cortex are affected in PwHD at the later stages of the disease, hence our results in this primate model, are in line with the pathological process observed in PwHD. Our EC findings provide valuable insights into the causal functional interaction changes occurring very early in this NHP model of HD.

Cortical Auditory Evoked Potentials in subjects with Mild Cognitive Impairment and Alzheimer's disease: a cross-sectional study taking hearing loss into account

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Alzheimer's disease (AD) is the most common cause of dementia, accounting for 60-70% of all dementia cases. Early diagnosis and follow-up of disease progression are important for timely interventions. Cortical Auditory Evoked Potentials (CAEPs) have shown promising results as an early indicator for cognitive decline and disease progression. CAEPs represent the neural activity in response to auditory stimuli and can be extracted from the ongoing electroencephalography (EEG) signal. These measurements offer several advantages, such as being non-invasive, cost-effective, and language-independent. However, it is important to note that hearing loss alters CAEP morphology similarly to cognitive impairment, i.e. prolonged peak latencies and reduced peak amplitudes. Hearing loss is common among older adults and a known risk factor for the development of dementia. Nevertheless, studies investigating the effect of both cognitive impairment and hearing loss on CAEP morphology are lacking. In this study, we aimed to evaluate the effect of cognitive impairment on CAEP components while correcting for hearing loss. This cross-sectional study included 54 subjects with mild cognitive impairment (MCI) or AD and 54 cognitively healthy control subjects matched for sex, age, and hearing levels. CAEPs were evoked using a classic auditory oddball paradigm, consisting of a frequent stimulus (1000Hz tone) with a probability of 80% and a rare stimulus (2000Hz tone) with a probability of 20%. The CAEP waveforms were compared between cognitively impaired and cognitively healthy subjects. In this study, no significant alterations in CAEP morphology were observed in subjects with MCI or AD when the effect of hearing loss was considered. Additional CAEP studies investigating the effect of both cognitive impairment and hearing loss are needed to confirm these findings and to investigate the effect of both on CAEP morphology.

Delta-MRI: a framework for direct deformation estimation from longitudinally acquired single-coil and multi-coil MRI data

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Longitudinal MRI is a key medical imaging tool for evaluating treatment effects, monitoring therapy and tracking disease progression over time. However, the time-consuming nature of MRI gives rise to long waiting lists and patient discomfort at every scan session. The primary focus of longitudinal MRI studies is to analyze temporal changes, such as structural deformations. This is typically achieved by reconstructing images from raw MRI data (the k-space) at multiple points in time and subsequently comparing them either qualitatively or quantitatively (e.g., volume measurements). Since longitudinal changes are naturally sparse and localized, significant redundancy exists between images of the same subject acquired at different time points. This temporal redundancy is hardly exploited in state-of-the-art methods. Indeed, most algorithms designed to shorten MRI scan times focus on cross-sectional imaging by exploiting spatial redundancy within a single time point.

We propose Delta-MRI, a framework that estimates longitudinal deformations directly from a baseline image and strongly undersampled k-space data of a follow-up scan. Preliminary results show that our approach has the potential to significantly accelerate follow-up scans without compromising deformation estimation quality, both with single-coil and multi-coil follow-up acquisitions.

SCREEN4PN: Efficient evaluation of therapeutic compounds for Charcot-Marie-Tooth disease using patient-derived induced motor neurons and neuromuscular organoids

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Charcot-Marie-Tooth (CMT) disease is the most common peripheral neuropathy, affecting over 2.5 million people worldwide. CMT exhibits an exceptionally broad clinical phenotype, complicating research into its pathophysiology. CMT1 primarily involves myelin degeneration, whereas CMT2 is marked by axonal degeneration. Both categories include multiple subtypes with distinct genetic causes, requiring the development of numerous animal models which hinders therapeutic development.

To address this challenge, we developed SCREEN4PN, a service platform that utilizes induced pluripotent stem cells (iPSC) for efficient drug testing on 2D and 3D cell models. We identified several pathological similarities across CMT phenotypes, enabling SCREEN4PN to facilitate therapeutic validations despite disease heterogeneity. Whereby the response to treatment can be evaluated using microscopy, qPCR, and protein biomarkers.

Utilizing patient-derived iPSCs along with isogenic and healthy controls, we can validate drugs, as well as personalized medicine approaches. These cells are differentiated into models tailored to specific subtypes. The 2D motor neuron model assesses axonal degeneration in CMT2, while the 3D neuromuscular organoid model facilitates myelin formation to study the CMT1 phenotype. Additionally, our cell banks undergo rigorous quality control to ensure standardized, high-quality cells for research and therapeutic applications in line with current GCP and industry standards.

So far, we have successfully completed two service contracts aimed at therapeutic compounds for CMT. In the future, we aim to expand SCREEN4PN to other diseases, optimize existing models, and incorporate advanced systems such as assembloids and microfluidics. By reducing the time, cost, and reliance on animal models using innovative approaches, SCREEN4PN offers a more ethical and efficient platform for pharmaceutical companies, clinical research organizations, and academic partners.

Multi-omics analysis reveals ischemic stroke-like features in matured hiPSC-deroved neurospheroids after oxygen-glucose deprivation/reoxygenation

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Despite the high global burden of ischemic stroke on patients and society, treatment options are limited and decades of research dedicated to finding new candidate neuroprotective drugs has not led to an effective neuroprotective therapy to date. This is partially due to the lack of appropriate model systems that recapitulate human ischemic responses in vitro. To address the shortcomings of these models, we developed a 5-month-old matured, bioreactor-based, hiPSC-derived neurospheroid model to more faithfully mimic adult neural tissue and its cellular interactions. Characterization of these neurospheroids showed presence of neurons, astrocytes and spontaneous electrophysiological activity. Notably, culturing these neurospheroids in a bioreactor reduced necrotic core formation typically present in organoids cultured for prolonged periods of time. To mimic ischemic stroke-like conditions, we exposed these neurospheroids to six hours of oxygen-glucose deprivation (OGD), followed by 72 hours of reoxygenation. The release of neurofilament-l, used as a marker for neuronal cell death, significantly increased in the OGD-exposed condition compared to the control. Additionally, analysis of untargeted transcriptomics and proteomics revealed upregulation of processes related to oxidative stress after 72h of reoxygation. Moreover, alterations in developmental and inflammatory signalling as well as a distortion of cellular metabolism and neurotransmission were detected. This translates to a loss of electrophysiological network activity as demonstrated by live cell Ca2+-imaging. In addition, we demonstrated the feasibility of incorporating immune cells known to play important roles in ischemic stroke, such as microglia, macrophages and neutrophils into these neurospheroids post-OGD. With this, we created a new model system to further investigate the neuroinflammatory cascade following ischemic stroke, which can help identify new targets for neuroprotection or repair.

Non-invasive site of collapse detection in obstructive sleep apnea patients

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Rationale: Differences in pharyngeal site-of-collapse influence efficacy of non-CPAP therapies for obstructive sleep apnea (OSA). Notably, complete concentric collapse at the palate (CCCp) during drug-induced sleep endoscopy (DISE) is associated with reduced hypoglossal nerve stimulation efficacy. Yet, CCCp is currently not recognisable using a clinical sleep study (polysomnography, PSG). Therefore, we developed a model to estimate DISE-based site-of-collapse using overnight PSG.

Methods: 182 OSA patients provided DISE and PSG data. Six polysomnographic flow-shape characteristics were identified as candidate predictors of CCCp (primary outcome, N=44/182). Multivariable logistic regression combined the six characteristics to predict clear presence (N=22) vs. absence (N=128) of CCCp. Odds ratios for actual CCCp were quantified after cross-validation. Secondary analyses examined complete lateral wall, tongue-base, or epiglottis collapse. External validation was performed on a separate dataset (Ntotal=466).

Results: CCCp was characterised by different flow shapes compared to non-CCCp. Odds ratio [95%CI] for CCCp in predicted positive vs. negative subgroups was 5.0[1.9–13.1]. The same characteristics provided significant cross-validated prediction of lateral wall (OR=6.3[2.4–16.5]), tongue-base (3.2[1.4–7.3]), and epiglottis (4.4[1.5–12.4]) collapse. CCCp and lateral wall collapse shared similar characteristics (skewed, scoopy), diametrically opposed to tongue-base and epiglottis collapse. External validation confirmed model prediction.

Conclusions: The current study provides a means to recognise patients with likely CCCp or other DISE-based site-of-collapse categories using routine PSG. As such, this model could facilitate clinical decision-making by making site-of-collapse information, associated with

treatment outcome, available without the need for invasive procedures. Furthermore, this model can be used to better understand OSA and within-night variation.

Unraveling how locus coeruleus activity mechanistically shapes brain network activity to govern context-dependent cognitive behavior

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The locus coeruleus (LC), a brain region in the brain stem, is a key regulator of exploration, attention and memory. Neuroimaging techniques have revealed that the LC can affect several brain networks to shift between different cognitive states such as exploration or attention. However, the specific connections between the LC and other brain regions enabling this cognitive flexibility remain elusive.

In this project, we aim to uncover i) how the LC directly influences other brain regions to shape specific cognitive processes and ii) how enhancement of LC activity causally influences other brain regions and thereby cognitive states in health and disease.

To this end, we will measure whole-brain activity in awake rats using non-invasive functional MRI on a 9.4 T MRI system. Structural connectivity between brain regions will be derived from diffusion-weighted MRI and used to infer model-based effective connectivity (EC) from functional MRI data. EC can discern causal influences brain regions yield over one another. These neuronal measures will be linked to behavioral paradigms assessing explorative behavior and novelty identification to uncover neural correlates of different cognitive states. First, we will assess which directed connections originating from the LC to other brain regions shape different cognitive states. Next, we will chemogenetically activate LC neurons to investigate how this affects EC and cognition in healthy rats. Lastly, we will enhance LC activity in a rat model for Alzheimer's disease, where the LC activity is known to be impaired through the disease, and assess if it can improve cognitive impairments.

By uniquely bridging the gap between cognitive behavior and how the LC causally reshapes brain activity, we will generate novel insights into the specific regulatory role of the LC in both health and disease which may eventually guide novel therapies to enhance cognition.

Integrating Neuropathology to Refine Genetic Risk in Alzheimer's Disease

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BACKGROUND: Alzheimer's disease (AD) is a heterogeneous disorder with a substantial genetic component. Traditional genome-wide association studies (GWAS) rely on clinical diagnoses of large cohorts, which are compromised by phenotypic heterogeneity. We conducted GWAS in a novel European neuropathological cohort (n=414) with detailed neuropathological characterization to identify genetic associations with specific AD-related lesions.

METHODS: AVITI low-coverage whole-genome sequencing was performed at 1x coverage. SNPs and indels were imputed using GLIMPSE2, referencing the 1000 Genomes Project panel. Association testing was conducted in PLINK2. Variants reaching genome-wide significance ($p < 5 \times 10^{-8}$) and notable subthreshold loci were evaluated for potential roles as quantitative trait loci (QTLs).

RESULTS: We identified genome-wide significant and suggestive loci contributing to the heterogeneity of AD risk. In addition to APOE, we discovered an intronic variant in GYPE and a variant upstream of ADAMTS16, both showed nominal associations with ABC score, reflecting AD pathology. Both were significantly linked to Braak staging (Tau neuropathological score), suggesting a potential role in tau-related lesions. Significant associations with co-morbidities were found, like granulovacuolar degeneration (necroptotic cell death), with an intronic variant in XAF1, and an intronic variant in NRF1 associated with Hirano body scores (actin aggregates).

CONCLUSIONS: Despite sample size constraints, we identified genome-wide significant associations with AD-related lesions by controlling for phenotypic heterogeneity. Results from QTL analyses highlight the molecular relevance of several loci and suggest potential novel risk genes. Moving forward, we will prioritize replication and meta-analysis in independent cohorts, functional validation and targeted resequencing.

Bridging the Gap Between Early Non-Invasive Markers and Neural Changes in Neurodegenerative Diseases

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Neurodegenerative diseases such as Alzheimer's Disease (AD) and Frontotemporal Degeneration (FTD) are major public health challenges, with a need for early, non-invasive markers to aid in diagnosis and monitoring. Recent research suggests that subtle changes in speech patterns could serve as an early indicator of these diseases. However, further research is needed to fully map speech changes associated with neurodegeneration and understand the underlying brain mechanisms driving these alterations.

This interdisciplinary project aims to link changes in speech to their neural origins by studying both human participants and mouse models of neurodegeneration. Mice communicate through ultrasonic vocalisations (USVs), while humans use speech – both of which will be analysed for changes in acoustic features and compared across species. From the insight gained from the acoustic changes, electrophysiological analyses will be applied to identify chaired disruptions in brain circuits.

By combining behavioural studies with neurophysiological investigations, this research seeks to uncover the neural basis of these early disease markers. Ultimately, identifying these connections could open new avenues for early diagnosis and therapeutic interventions, with the goal of slowing disease progression before significant cognitive symptoms develop.

Dissecting ABCA7's role in Alzheimer's Disease Through Microglial Transcriptomics

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The ATP-binding cassette subfamily A member 7 (ABCA7) gene, initially identified as a major risk factor for Alzheimer's disease (AD) through genome-wide association studies (GWAS), exhibits a distinct expression pattern in the brain with the highest expression levels found in microglia. Previous studies indicated ABCA7's involvement in microglial phagocytosis. We aimed to examine how changes in ABCA7 expression in microglia impact gene expression between phenotypes and between microglial subtypes across phenotypes. We performed single-nuclei RNA sequencing (10X genomics) on the BA10 region of nine ABCA7 mutation carriers, six AD non-carriers and eight cognitively healthy controls. After integration with RPCA, harmony and ambient RNA removal with DecontX, microglia were isolated. We performed subtyping of the microglia with the FindMarkers function from Seurat. We could identify homeostatic, ribosomal response, disease associated, cytokine response, antigen presenting response and neuronal marker microglia. We see differences in cell type proportions between the three different phenotypes. Preliminary analysis revealed promising differentially expressed genes. Eventually we will link these changes in gene expression to pathways that could link ABCA7 to AD risk and further decipher the role of microglia in AD.

Resting-State Co-Activation Patterns in Pre-Dementia Alzheimer's Disease Patients: A Potential Early Marker?

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Alzheimer's disease (AD) is the most common neurodegenerative disorder, leading to cognitive decline, dementia, and death. It is marked by amyloid beta accumulation and neurofibrillary tangles of hyperphosphorylated tau, disrupting synaptic function and contributing to cognitive impairment. AD progresses through stages, from preclinical AD (biomarker evidence without symptoms) to prodromal AD (mild cognitive impairment with preserved daily function).

Resting-state fMRI (rs-fMRI) assesses whole-brain functional connectivity (FC) by measuring synchronized activity across regions. Traditional static FC analyses reveal reduced network efficiency, particularly in the default mode network (DMN), while dynamic FC captures temporal fluctuations, offering a more sensitive measure. Large-scale co-activation patterns (CAPs) provide deeper insights into resting-state brain dynamics.

The EPAD database, a multi-center cohort of 1,500 non-demented individuals, includes neuroimaging, CSF biomarkers, and neuropsychological data. A recent study using eigenvector centrality highlighted alterations in early AD. CAP analysis, as a complementary approach, offers novel insights into AD-related network dysfunction by comparing CAP metrics in healthy controls and pre-dementia AD. This study aims to advance understanding of CAPs in AD and assess their potential as early biomarkers for disease detection and progression.

Unravelling SAA-mediated immune responses to bacterial-derived amyloids in the central nervous system

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Recent studies indicate that gut inflammation can exacerbate the risk of developing Alzheimer's Disease (AD). Our lab found that bacterial amyloids act as potent immune inducers in the gastro-intestinal tract and its enteric nervous system (1). In this context, serum amyloid A3 (SAA3) emerged as a key regulator driving a pro-inflammatory feed-forward response, characterized by cytokine secretion and T-cell infiltration. Since SAAs are acute-phase proteins with pro-inflammatory and amyloidogenic properties, which are elevated in the brains of AD patients, we asked whether they play a role in pathogenic gut-brain communication in AD. To investigate this, we administered intraperitoneal injections of the bacterial amyloid curli in C57Bl6 mice. This caused a general increase in circulating SAA protein levels and a specific, restricted elevation of Saa3 expression at brain borders. As a more direct means to interrogating the putative function of SAAs in AD pathology progression, we stereotactically injected adeno-associated viral vectors that cause constitutive Saa3 expression into the hippocampus of one-month-old APP/MAPT mice. Through RNA-Scope and quantitative immunofluorescence staining, we will evaluate the impact on microglial activation and Aß load, respectively. Lastly, we are investigating whether this SAA loop is conserved in humans by exposing iPSC-derived microglia progenitor cells to curli and Aß. Preliminary results indicate that these cells produce SAA1/2 in response to curli, making them a good human model to further investigate. By uncovering the role of SAAs in early immune-driven mechanisms of AD pathogenesis, we aim to provide novel insights that contribute to the development of disease-modifying therapies for this devastating disorder.

(1) Verstraelen et al (2024). CMGH, 18(1), 89–104.

Longitudinal in vivo assessment of tissue alterations and synaptic density as non-invasive biomarkers for traumatic spinal cord injury

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Traumatic spinal cord injury (SCI) can lead to severe and lasting difficulties in movement and sensation, significantly affecting quality of life. Predicting recovery outcomes remains challenging due to the lack of reliable biological markers. My research explores how advanced imaging techniques could provide new insights into the progression of SCI and help predict recovery.

Using a rat model of cervical SCI with varying injury severities, we followed the healing process over six weeks with two types of imaging: MRI to visualize tissue damage and PET scans to assess changes in synaptic connections. MRI scans allowed us to measure the size of the injury and detect tissue alterations, while PET imaging targeted a specific protein (SV2A) involved neurotransmitter release and synaptic function. We also monitored the rats' motor skills to see how their functional recovery correlated with the imaging findings.

Our results showed that larger injuries caused more tissue damage and greater loss of synaptic connections. Although the injury size decreased over time, the extent of damage remained related to the initial severity of the injury. The combined imaging methods provided a comprehensive view of both structural and functional changes following SCI.

This study highlights the potential of MRI and PET imaging as non-invasive tools to track spinal cord injury progression. These techniques could play a key role in developing better ways to predict recovery and test new treatments for patients with SCI.

Postural responses to otolith-specific gait tasks in vestibular patients

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Introduction: The otoliths end-organs, part of the vestibular system, detect roll tilt and linear acceleration including gravity. We hypothesized that otolith-specific balance tasks, such as a sudden freeze of gait, reversals of gait after walking forward, and head tilts during static standing are mediated by otolith function. This study aimed to investigate postural responses to these tasks in healthy adults and individuals with vestibular hypofunction.

Methods: In this cross-sectional study, healthy adults and vestibular patients performed static and dynamic otolith-specific tasks: standing with a head tilt, sudden freezes of gait , and instant reversals from forward to backward walking. Participants wore inertial measurement units (IMU), and in the vestibular patients and additional analysis using a 3D pose estimation model was collected. Postural responses were compared between groups. The relationship between objective postural responses and otolith function will be examined using IMU and 3D pose model data, which will be fully processed by the end of February 2025.

Results: Twelve vestibular patients (62.6 ± 9.8 years, 5 women) and 13 controls (35.6 ± 11.5 years, 4 women) participated. Compared to controls, vestibular patients walked slower overground (2.7 vs. 3.2 mph, $p=0.007$) and on a treadmill (2.6 vs. 3.1 mph, $p=0.015$), with worse freeze and reverse responses, including more corrective steps and increased fall risk. Vestibular patients could stand as long as the controls on foam with eyes closed and contralesional head tilt ($p=0.168$) with a but stood significantly shorter with an ipsilesional tilt ($p<0.001$).

Discussion: Vestibular patients experience greater difficulty with otolith-specific tasks, particularly with ipsilesional head tilts, likely due to otolith-spinal pathway dysfunction.

From GWAS to Function: Prioritizing Genes in Neurodegenerative Brain Disease Risk Loci through Cell-type-specific Transcript eQTL Mapping

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Neurodegenerative brain diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), Amyotrophic Lateral Sclerosis (ALS), sporadic Creutzfeldt-Jakob disease (sCJD), and frontotemporal lobar degeneration (FTLD) impose a substantial burden on individuals and their families. While genome-wide association studies (GWAS) have identified numerous disease-associated variants, most lie in non-coding regions, making their functional relevance unclear. For my thesis, I aim to prioritize genes near lead variants associated with various neurodegenerative brain diseases making use of expression quantitative trait loci (eQTLs), which are variants that influence the expression of nearby genes—potentially mediating phenotypic effects.

I started by analysing genotyping array data (Illumina Infinium™ Global Screening Array-24 v3.0) from individuals with and without AD. Following stringent quality control and genotype imputation via the TOPMed R3 reference panel, I extracted genetic data for the GWAS lead variants of the previously mentioned neurodegenerative brain diseases. I then integrated these genotypes with long-read single-nucleus RNA-sequencing data from human brain tissues to perform transcript-level cell-type-specific eQTL (transcript-ct-eQTL) mapping.

The transcript-ct-eQTL mapping showed potential cell-type-specific regulatory effects of the GWAS lead variants of the five diseases. One example is the FTLD- and AD-associated lead variant rs5848, which showed a significant association ($P = 0.001$) with expression of the ENST00000587109 transcript of the GRN gene in GABAergic neurons.

This integrative approach prioritizes genes through transcript-ct-eQTL mapping to shed light on the functional implications of disease-associated genetic variants on brain transcript diversity, not only for AD but for other neurodegenerative brain diseases as well.

Understanding KCNQ2-encephalopathy: Leveraging human stem cell-derived neuronal models to uncover disease mechanisms and develop therapeutic solutions

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KCNQ2-encephalopathy caused by pathogenic gain-of-function variants in the KCNQ2 gene, is a severe neurological disorder that manifests in early childhood. It is characterized by developmental delay, intellectual disability, difficulties in movement and speech and autism spectrum disorder, significantly impacting the quality of life for both affected children and their families. Currently, the mechanisms by which these genetic changes lead to neurodevelopmental disorders remain largely unexplored and there are no specific treatments available for these patients. Therefore, this project aims to investigate how KCNQ2 gain-of-function variants lead to these severe neurological conditions. By integrating state-of-the art human induced pluripotent stem cell (hiPSC)-derived neuronal cell cultures with multi-electrode array recordings, we demonstrate that mutant KCNQ2 neurons exhibit delayed electrical maturation and reduced neuronal network activity compared to controls. Additionally, we aim to combine the power of these hiPSC-derived neurons and electrophysiological read-outs together with transcriptome sequencing and computational predictions to develop a drug screening platform to repurpose well-characterised clinically-approved drugs. This approach will offer new perspectives on the pathology of KCNQ2-encephalopathy and drive the discovery of novel therapeutic candidates.

Targeting axonal transport defects in Charcot-Marie-Tooth disease type 2J

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Affecting approximately 1 in 2500 individuals worldwide, Charcot-Marie-Tooth disease (CMT) is the most prevalent inherited peripheral neuropathy. Patients present with a range of symptoms from progressive muscle weakness to sensory loss and pain. This clinical variability is reflected in its genetic heterogeneity, with mutations in over 100 genes identified to date. The lack of effective treatments for CMT underscores the importance of identifying common disease mechanisms across subtypes to guide therapeutic development.

One potential unifying mechanism in CMT is the involvement of axonal transport defects. Axonal transport is the process whereby motor proteins traverse microtubule networks within axons to bi-directionally deliver essential cargoes (e.g., organelles, RNAs and proteins) between the neuronal cell body and distal axon terminals. Defective axonal transport has been implicated in many neurodegenerative diseases, including CMT.

We recently generated and characterized a mouse model for CMT2J, a late-onset subtype marked by axonal degeneration, and found indications of impaired axonal transport through in vivo imaging of endosomal trafficking in peripheral nerves. We repeated this experiment, now including CMT2J mice lacking histone deacetylase 6 (HDAC6) – an emerging therapeutic target for CMT subtypes marked by axonal transport dysfunction. Interestingly, these mice's endosome dynamics resembled those of wild-type mice, indicating that HDAC6 could be a promising target to rescue axonal transport defects and degeneration in CMT2J.

To extend these findings, we are developing 3D in vitro models to replicate the peripheral nervous system (PNS). Briefly, induced pluripotent stem cells from CMT2J patients are differentiated to motor neuron spheres and fused with muscle spheres. This mimics the directional growth and interactions of the PNS and would allow the investigation of defective pathways and test potential therapeutics for CMT2J, like HDAC6 inhibitors.

The study of alpha-synuclein pathology and related neuroinflammation in a human brain-like context: a human neurospheroid approach

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Synucleinopathies, including Parkinson's disease, are neurodegenerative disorders characterized by the formation of alpha-synuclein (αSyn) aggregates that propagate prion-like between nervous system cells. The exact role of αSyn pathology in disease progression remains unclear. Moreover, how microglia precisely affect αSyn pathology remains to be elucidated. Current in vitro models are limited in their ability to faithfully replicate human responses to pathological αSyn.

In my research, I will use human neurospheroids (NSPHs) to enhance our understanding of αSyn pathology, more specifically the pathophysiological pathways associated with αSyn accumulation. By using NSPHs with and without microglia, I aim to clarify the role of microglia and neuroinflammation in general in αSyn accumulation and downstream cellular responses. Hereto, pre-formed αSyn fibrils will be added to NSPHs and αSyn accumulation will be monitored over time by staining NSPHs for pathological αSyn. Next, pathways elicited with αSyn accumulation will be determined at the transcriptome and proteome level and further characterized at the cellular and functional level, by means of immunocytochemistry and functional assays (e.g. calcium imaging), respectively.

In summary, this research project will help to identify pathophysiological mechanisms associated with αSyn pathology possibly leading to neuronal dysfunction or loss, and clarify the role of microglia, in a human brain-like context.

Defining the role of nuclear envelope stress in glioblastoma

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Glioblastoma (GBM) is the most common and aggressive primary brain tumor, with a median survival of only 15 months after diagnosis and no cure. A key challenge in treating GBM is its heterogeneity, as glioma stem-like cells (GSCs) can self-renew, change phenotype, and interact with the surrounding tumor microenvironment. While intensive GBM research has revealed a variety of molecular alterations, less attention has been given to the altered biophysical properties. Yet, GSCs experience vastly different mechanical forces than their non-transformed counterparts. We and others have found that these forces cause nuclear envelope (NE) stress, disrupting cell homeostasis, and triggering DNA damage and inflammation. To understand the impact of NE stress on GBM aggressiveness, we are now investigating how GSCs respond to mechanically induced NE stress and to what extent their vulnerability to NE stress correlates with cell state plasticity. To do so, we have first documented the levels of crucial NE stress regulators such as lamins in a panel of patient-derived GSCs. This revealed that the level of Lamin A/C was the highest in a more aggressive GSC cell line. Next we have implemented a mechanical compression paradigm, which we calibrated with astrocytoma cell lines stably expressing two NE stress reporters (BAF and cGAS). We found that both reporters mobilize rapidly to NE lesions, but demonstrate distinct dissolution kinetics. We also found that depleting A-type lamins sensitizes cells to significant NE stress at a moderate confinement level, underscoring their significance. Subsequently, we are evaluating the impact of mechanical confinement on NE stress in the panel of GSCs and exploiting the reporter system for in-depth proteomics analysis to unveil putative novel NE stress regulators. This way, we intend to increase our understanding of GBM pathology progression and contribute insights that could open novel therapeutic avenues for this devastating disease.

Development of a 2D Co-Culture System to Uncover Schwann Cell-Macrophage Interactions in CMT1A

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Charcot-Marie-Tooth (CMT) disease is the most common inherited peripheral neuropathy, with the majority of cases being caused by a duplication of the peripheral myelin protein 22 (PMP22) gene. PMP22 is an integral membrane glycoprotein of compact myelin, which is strongly expressed by Schwann cells (SCs). Increasing evidence indicates a critical role of the immune system in the disease pathology, and especially macrophages have been linked to CMT1A disease progression. However, the specific mechanisms by which macrophages interact with Schwann cells and influence the disease remain unknown. Therefore, we aim to investigate the intricate interplay between Schwann cells and macrophages to elucidate the underlying disease mechanisms of CMT1A. Currently, we are optimizing a 2D co-culture system to explore direct and indirect interactions between Schwann cells and macrophages in CMT1A. To clarify cell-cell interactions, Schwann cells and blood-derived macrophages from CMT1A patients or healthy controls are co-cultured for 72 hours. In addition to the co-culture experiments, macrophages are also stimulated with conditioned culture medium of healthy and CMT1A Schwann cells to study indirect signaling effects. Our focus will be to identify potential key targets and mechanisms involved in Schwann cell and macrophage interaction and communication. In summary, the establishment of a 2D co-culture system will provide a powerful platform to unravel the molecular mechanisms driving Schwann cell / macrophage interactions in CMT1A. Insights gained from this study will advance our understanding of neuro-immune crosstalk in peripheral neuropathies and may uncover novel therapeutic strategies targeting immune responses in CMT1A.

TMEM106B Loss-of-function dysregulates the pre-synaptic proteome in human iPSC-derived cortical neurons

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TMEM106B haplotypes have been found to modulate the risk for several neurodegenerative diseases such as Frontotemporal lobar degeneration with TDP-43 aggregates and were shown to impact healthy aging and neuronal reserve, suggesting that they determine neuronal vulnerability. These haplotypes are thought to regulate the expression levels of TMEM106B, a lysosomal type-II transmembrane protein, with a slight increase in expression associated with the risk haplotype. However, the mechanisms through which TMEM106B exerts its pathogenicity remain unclear.

We generated full TMEM106B knockout (TMEM106B-/-) iPSC-derived cortical neurons. We performed whole cell mass spectrometry of these neurons at DIV80. We also analyzed lysosomal trafficking with live cell imaging and lysosomal enzymatic activity. In order to have fully mature, spine-bearing neurons, we xenografted neuronal precursor cells in immunodeficient mice and analyzed the cell ramification, spine density and synaptic content of the neurons at 9 months old.

We observed a downregulation of proteins involved in synaptic vesicular metabolism and transport and an upregulation of galectin-3, a marker for lysosomal damage, suggesting alterations of the endolysosomal pathway. We confirmed a significant loss on presynaptic markers and increase on lysosomal markers in the TMEM106B-/- neurons by western blot. Moreover, functional characterization of endolysosomal fitness showed reduced lysosomal trafficking, lysosomal accumulations in the soma and dysregulated cathepsin D activity.

Our results show that loss of TMEM106B leads to a dysregulation of the presynaptic terminal and the endolysosomal system, pointing towards a dysfunction in the recycling or docking of these vesicles. This would indicate a direct role of TMEM106B in the maintenance of healthy presynaptic compartments, and could explain how TMEM106B dysregulations affect neuronal vulnerability.

Therapeutic strategies in demyelinating neuroinflammatory disorders of the central nervous system

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Background. Immune-mediated demyelinating disorders of the central nervous system (CNS) are a neuroinflammatory spectrum of which multiple sclerosis (MS) is the most frequent disease. Other rarer diseases are neuromyelitis optica spectrum disorders (NMOSD) and myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD), which have a poorer prognosis for clinical recovery following attacks. Overall, maintenance treatment aims to modulate and/or suppress the immune system so as to avoid attacks and disability accrual.

Objectives. This doctoral project aims to explore therapeutic strategies in MS and related neuroinflammatory disorders through targeted studies.

Methods. A modified Delphi panel process comprising MS experts, patient and industry representatives will attempt to reach consensus-based definitions of a “cure” for MS. Immune reconstitution therapies (IRTs), which are treatment options for aggressive MS, will be compared considering their efficacy to control disease activity and disease progression, used as first-line versus later-line treatment in a retrospective observational cohort study using data from the largest international MS registry, MSBase. Furthermore, a retrospective cohort study on NMOSD collecting data from multiple Belgian medical centres, will be performed to provide a comprehensive description of NMOSD patients in Belgium and further our understanding of their demographic, clinical, paraclinical and treatment characteristics. Additionally, a modified Delphi panel method including international leading experts on NMOSD will be conducted following their case-based NMOSD/MOGAD meeting in 2024, which focused on mitigation strategies of infectious risk in NMOSD.

Conclusion. This doctoral project will contribute to the advancement of current knowledge on treatment management of neuroinflammatory disorders of the CNS to the benefit of the scientific community and the patients.

Exploring the impact of somatic instability in Huntington's disease on tissue microstructure using in vivo MRI

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Huntington disease (HD) is a genetic neurodegenerative disorder characterized by a triad of motor, cognitive and psychiatric symptoms. It is caused by a CAG repeat expansion in the Huntingtin (HTT) gene, leading to the production of a misfolded protein, mutant huntingtin (mHTT). As a result, the pathological hallmark of HD is the aggregation of mHTT, which initiates in the striatum leading to neuronal dysfunction and death. Even before the onset of visible brain changes, subtle microstructural damage to white matter pathways occur, potentially 15 years prior to symptoms.

The temporal course of neurodegeneration in HD is largely determined by somatic instability (SI), the progressive somatic expansion of CAG repeats, rather than solely by the inherited CAG repeat length of ~40 which ensures HD onset. Recently, the Msh3 gene has emerged as a regulator of SI and its suppression leads to reduced mHTT protein aggregation in striatal neurons, making it a promising therapeutic target.

However, the precise effects of SI on brain structure remains unclear. To address this, we will explore the spatiotemporal structural changes in the Q111 mouse model of HD. This will be achieved by high-resolution anatomical 3D MRI and advanced multi-shell diffusion MRI to capture the macro- and microstructural deficits along with the novel inhomogeneous magnetization transfer (ihMT) MRI contrast, to dissect white matter integrity. This technique enhances the visualization of myelin rich tissues by isolating interactions of the restricted macromolecules in the myelin sheath and surrounding water.

By integrating in vivo MRI with myelin histology, this project will be the first one to explore how targeting SI impacts brain structure. The results will provide crucial insights for developing innovative therapies for HD and other trinucleotide repeat disorders.

Effectiveness of an eHealth self-management support program for persistent pain after breast cancer treatment: a study protocol

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Background: Persistent pain following breast cancer treatment is a prevalent problem and poses significant challenges for patients' quality of life. The current state-of-the art advocates for a biopsychosocial rehabilitation approach integrating pain science education with self-regulation techniques to promote an active lifestyle. However, accessibility and costs remain barriers to effective pain self-management support. An eHealth self-management support program presents a promising solution, providing a multidimensional support model. The aim of this study is to investigate the effectiveness of an eHealth self-management support program for pain-related disability in breast cancer survivors with persistent pain.

Methods: Through a 3-arm multicentric RCT, a total of 270 breast cancer survivors with persistent pain will be randomized into three groups: an eHealth intervention group, a face-to-face group in a physical therapy setting and a usual care group. Primary outcome is self-reported pain-related disability (Pain Disability Index) 6 months after baseline. In addition, pain, physical, emotional and socio-economical functioning will be evaluated as secondary outcomes up to 12 months after baseline.

Results: The study aims to establish the superiority of the eHealth self-management support program over the usual care intervention and non-inferiority compared to the face-to-face program for persistent pain-related disability after breast cancer treatment.

Conclusion: The findings of this study could hold significant implications for improving the management of persistent pain after breast cancer treatment. By using eHealth technology, the program addresses key barriers, including accessibility, cost, and patient engagement. Furthermore, this program allows for tailored interventions that cater to the diverse biopsychosocial needs of patients. Successful implementation of the eHealth program could be the solution in pain management in this population.

Individualized Optimization of Mandibular Advancement Devices in Obstructive Sleep Apnea: A Clinical Outcome Analysis

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Introduction:
The mandibular advancement device (MAD) is an established OSA treatment, typically titrated subjectively based on patient symptoms such as snoring or daytime sleepiness. However, subjective improvement may lead to premature titration termination. This study evaluates whether objective titration via polygraphy can improve treatment outcomes.

Methods:
All patients started MAD therapy for three months (ProSomnus MAD EVO Device) as a first-line treatment option. The MAD was fitted in the maximum comfortable protrusion minus 3 millimeters. Titration was guided based on subjective relief of cardinal symptoms. The efficacy of the therapy in terms of reduction in OSA severity was evaluated by polysomnography (PSG). Response was defined as AHI with MAD<10 events/hour. In non-responders (AHI with MAD>10 events/hour), additional titration under polygraphic guidance (MediByte) was performed. Differences in respiratory parameters (AHI, oxygen desaturation index (ODI) and sleep apnea specific hypoxic burden (SASHB)) between responders and non-responders were evaluated.

Results:
86 patients completed the study of which 73 patients could be considered responder based on subjective titration solely, while 13 patients (male: 100%; age: 55±11 years; BMI: 28.0±4.4 kg/m²) needed additional titration based on AHI>10/h on PSG.

In the responder group, AHI, ODI and SASHB improved significantly under MAD therapy. In the non-responders who needed additional titration, the respiratory parameters AHI, ODI and SASHB improved following optimization. AHI, ODI, and SASHB were significantly higher at baseline ($p<0.05$) and after subjective titration ($p<0.05$) in the non-responders vs responders, but became comparable after optimization.

Conclusion:
Our findings indicate that subjective titration may not be sufficient for guiding MAD therapy. Further objective optimization can result in improved MAD treatment outcomes.

Co-activation pattern analysis on resting-state fMRI data in people with Huntington's Disease

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Huntington's Disease (HD) is a neurodegenerative disorder caused by an inherited monogenic autosomal dominant mutation, namely a cytosine-adenosine-guanine (CAG) trinucleotide repeat expansion in the Huntingtin (HTT) gene. The CAG expansion encodes for a long poly glutamine tract, leading to the production of mutant HTT (mHTT) protein, toxic and prone to aggregate. Due to a selective vulnerability of the medium spiny neurons to mHTT, normal striatal functioning is disrupted, which eventually leads to movement dysfunction. Resting state functional MRI (RS-fMRI) can be used to capture fluctuations in spontaneous neural activity via the blood oxygenation level dependent (BOLD) contrast. Distant brain regions show high temporal correlations, referred to as functional connectivity (FC), between their BOLD signals forming resting state networks (RSNs). Temporal fluctuations in FC can be observed within these networks and have been shown to be altered in some neurodegenerative diseases. However, no study has investigated the temporal fluctuations in the brain's functional dynamics in people with HD (PwHD). We plan to bridge this gap by using co-activation patterns (CAPs), which are transient sub-components of RSNs and have proven to accurately distinguish in between HD model mice and wild type mice. In this project, RS-fMRI scans were made with a 3 T Magnetom ALLEGRA (Siemens) head MRI system on a population sample of healthy controls (n=56), pre-manifest patients (n=23) and manifest patients (n=32). We aim to extract CAPs and their metrics from controls and PwHD, to compare spatial and temporal properties of the identified CAPs and to feed the CAP metrics into a classifier to train it to accurately predict the disease state in individual participants.

Is autonomic function associated with (central) pain processing in individuals with chronic pain? A systematic review.

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Background and aims: Dysfunctions of the autonomic nervous system (ANS) are hypothesized to be associated with altered central pain processing (CPP). Altered CPP characterizes nociplastic pain, which is common in non-specific chronic pain conditions. However, the exact interaction between ANS function and chronic pain remains unclear.

Methods: PubMed, SCOPUS, and Web of Science were searched, followed by a two-phased screening by two independent researchers (IM & CQ). Risk of bias (Newcastle-Ottawa Scale), level of evidence and data collection were performed double-blind.

Results: Two cohort studies, 10 cross-sectional studies, and one case-control study were included. ANS function was measured by cardiovascular measurements, sympathetic skin response, plasma catecholamines, and skin temperature. All studies used questionnaires to assess pain, nine used additional quantitative sensory testing. Significant associations between autonomic function (heart rate and blood pressure) and pain intensity (VAS) were found in patients with Irritable Bowel Syndrome ($p<0.05$). Patients with chronic musculoskeletal pain showed significant associations between conditioned pain modulation and cardiac autonomic response ($p=0.002$) and increased hyperalgesia ($p<0.01$). Conflicting evidence was found for patients with Complex Regional Pain Syndrome and fibromyalgia. No significant associations were found in patients with chronic Whiplash Associated Disorders and chronic pancreatitis.

Conclusion: There was heterogeneity in ANS and pain measurements, creating a pitfall to provide a qualitative comparison of results. Therefore, this review provides insight into the potential involvement of autonomic pathways in pathological pain mechanisms in several chronic pain populations, but clearly urges the need for standardized measurements.

Assessing non-invasive quantitative methods for [^{18}F]SynVesT-1 PET imaging of synaptic vesicle glycoprotein 2A in the rat brain

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Understanding how brain cells communicate is crucial for studying neurological diseases like Alzheimer's disease, epilepsy and spinal cord injury. Therefore, brain imaging techniques, such as PET scans, can be used to measure synaptic density—the number of connections between neurons. A specific PET tracer, called [^{18}F]SynVesT-1, binds to synaptic vesicle glycoprotein 2A in the synapses and can be used to visualize these connections. However, its application in rats has not been explored. Accurate quantification of PET images in small rodents also requires arterial blood sampling, which is an invasive procedure.

Therefore, our study aimed to validate quantification methods to measure synaptic density in rats using [^{18}F]SynVesT-1. First, different kinetic modelling methods were investigated to accurately quantify synaptic density. Then, the use of two image-derived input functions was assessed as non-invasive alternatives to the arterial blood sampling.

Our results showed that the 2-tissue compartmental model and Logan plot fitting (two kinetic modelling methods) were able to provide a good fit for this tracer in rats. Additionally, both non-invasive image-derived approaches were found to be good alternatives to invasive arterial blood sampling. This means that synaptic density in rats can be quantified with [^{18}F]SynVesT-1 PET imaging without the need for invasive blood sampling, making future studies more efficient and less stressful for the animals. Ultimately, our findings contribute to advancing brain imaging techniques and improving preclinical research on neurological disorders.

The Birth of Connections: How Embryonic Progenitor Diversity Shapes Striatal Circuitry

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The organization of synaptic connections in neural circuits is fundamental to brain function, yet the developmental processes shaping their formation remain poorly understood. Increasing evidence suggests that embryonic neural progenitor diversity influences neuronal diversity, synaptic connectivity, and circuit function. My research investigates how distinct progenitor populations in the lateral ganglionic eminence—specifically apical intermediate progenitors (aIPs) and other progenitors (OPs)—influence the synaptic architecture of the striatum, a brain region critical to movement, learning, and cognition.

Using a powerful combination of in utero electroporation, viral tracing, optogenetics, and single-cell RNA sequencing, I've mapped the input-output relationships of striatal spiny projection neurons (SPNs) derived from different progenitor lineages. My findings reveal that aIP-derived SPNs receive extensive innervation from both cortical and thalamic sources, with 32% of thalamic inputs originating specifically from the intralaminar nuclei. Functional optogenetic mapping has uncovered significant biases in connection strength based on developmental origin, with aIP-derived SPNs showing markedly reduced excitatory responses compared to OP-derived neurons when stimulating parafascicular inputs. Single-cell transcriptomics has identified LHX9 as a candidate transcription factor potentially mediating these connectivity differences. My ongoing work aims to manipulate LHX9 expression to determine its role in synaptic partner selection and dendritic architecture. This research illuminates how developmental lineage influences circuit assembly in the striatum, potentially revealing fundamental principles of circuit formation with implications for understanding both normal brain function and neurodevelopmental disorders.

Hexanucleotide repeat expansions in C9orf72 impair microglial activation and result in a defective glial response in ALS

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Although the involvement of microglia in amyotrophic lateral sclerosis (ALS) is recognized, the precise underlying molecular mechanisms remain elusive. We generated single nuclei transcriptomic profiles from the spinal cord and motor cortex of sporadic (sALS) and C9orf72 (C9-ALS) ALS patients. We confirmed that C9orf72 is highly expressed in microglia and observed that the hexanucleotide repeat expansion (HRE) results in haploinsufficiency specifically in these cells. Whereas sALS microglia transitioned towards disease-associated profiles, C9orf72 HRE microglia exhibited a diminished response, with deficits in phagocytic and lysosomal pathways. We confirmed these lysosomal alterations in cortical and spinal cord tissue, as well as in C9orf72-deficient induced pluripotent stem cell (iPSC)-derived microglia, with a disrupted lysosomal distribution and an increased number of intracellular structures consistent with storage lysosomes. Furthermore, we observed a diminished response of astrocytes in C9orf72 HRE carriers and found that spinal astrocytes are distinct from cortical astrocytes and show a particular enrichment for ALS upregulated genes. We provide in silico

predictions pointing to altered cell-cell interactions between microglia and astrocytes. This complex interplay highlights possible variations in cellular responses between sporadic and inherited ALS variants, providing valuable insights for patient stratification and for selecting appropriate treatments.

Validation and non-invasive kinetic modelling of [18F]BCPP-EF PET imaging in mice

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Huntington's disease (HD) is a hereditary, progressive neurodegenerative disorder with diverse clinical manifestations that evolve as the disease progresses. The main symptoms of HD are motor dysfunctions, mood disturbances and cognitive difficulties. In HD, the cellular respiratory ATP production is defective, leading to neuronal death. The mitochondrial respiratory chain (MRC), which plays a crucial role in respiratory ATP production, is located on the inner mitochondrial membrane and consists out of five mitochondrial complexes. Among these, mitochondrial complex I (MC-I) is the largest and serves as the primary entry point for electrons into the MRC, ultimately contributing to the electrochemical gradient required for ATP synthesis. Therefore, deficiencies in MC-I function lead to impaired cellular energy production and increased oxidative stress. These deficiencies can be detected using positron emission tomography (PET), a non-invasive in vivo imaging technique that can be used for the assessment of disease progression or therapeutic effects through the administration of radiolabelled tracers targeting affected molecular compounds. The aim of this study is to validate the [18F]BCPP-EF PET radiotracer, which targets MC-I, for first time use in mice. This will be done by evaluating four main aspects of the tracer: 1) characterization of the radiometabolite profile; 2) evaluation of the volume of distribution and assessment of tracer kinetics using compartmental modelling; 3) analysis of the variability and reliability of tracer quantification; 4) assessment of tracer specificity to MC-I. Successful validation of this tracer will enable its use in future studies to monitor disease progression and assessing the efficacy of therapies targeting MC-I.

Investigating the effect of histamine hypofunction on the development of the bed nucleus of the stria terminalis (BNST) and Tourette's syndrome (TS)

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Tourette's syndrome (TS) and obsessive-compulsive disorder (OCD) are neurodevelopmental disorders affecting approximately 0.6% of the population. While their exact causes remain unclear, severe cases have been linked to mutations in the Hdc gene, the enzyme responsible for histamine production and patients with this mutation are seen to exhibit lowered histamine levels. While generally seen as disorders of the basal ganglia, both TS and OCD show a strong social component where stress and anxiety can reduce the ability to suppress tics. A key brain region in regulating stress and anxiety is the bed nucleus of the stria terminalis (BNST), which receives strong histaminergic input (Marquez-Gomez et al. 2023). We hypothesize that the BNST is a critical hub in the emergence of TS and OCD symptoms and that its development is altered by reduced histamine levels. To investigate this, we are developing a novel pharmacological mouse model of histamine hypofunction, in which histamine levels are reduced transiently during critical windows in brain development. Preliminary data from our lab shows that reduced levels of histamine during embryonic development significantly alter cell-cycle kinetics in embryonic brain regions giving rise to both BNST and striatal neurons, suggesting that transiently lowered histamine levels may impact the formation of brain circuits.

The effectiveness of a structured exercise program in preventing chemotherapy-induced peripheral neuropathy: protocol for a randomized controlled trial

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Chemotherapy-induced peripheral neuropathy (CIPN) is a prevalent side effect of neurotoxic cancer treatment. The most common CIPN symptoms are sensory and motor symptoms in the hands/feet. CIPN can interfere with daily activities and cancer treatment. While exercise might alleviate symptoms, evidence quality is low, so it is not included in international guidelines for CIPN prevention (as no other strategy). Additionally there is limited knowledge on the barriers and facilitators of exercise programs during chemotherapy treatment for the prevention of CIPN. This knowledge is essential for optimizing exercise interventions and adherence, and integrating exercise into clinical practice for CIPN prevention. Therefore, the primary goal of this project is to study the effect of an exercise program on symptoms of CIPN in breast and colon cancer patients receiving taxane- or platinum-based chemotherapy. The exercise program is patient-tailored based on exercise guidelines in oncology. A prospective randomized controlled trial with short (3 months) and long-term (6 months) follow up will be conducted with self-reported CIPN symptoms (QLQ-CIPN20, sensory subscale) as primary outcome. Secondary scientific objectives are the effect of the exercise program on CIPN signs (objective evaluation), physical (self-reported and objective evaluation), mental and social functioning (self-reported) and relative dose intensity of chemotherapy (objective evaluation). Tertiary scientific objective is to perform a process evaluation. The aim of this process evaluation is to investigate the barriers and facilitators of the exercise program in patients receiving taxane- or platinum-based chemotherapy by examining adherence to the exercise program as well as how patients and healthcare providers perceive the implementation of the

exercise program. Such process evaluation may aid in identifying determinants of exercise program attrition and offering recommendations for valorisation.

Exploring the role of the immune system in a model of Helsmoortel-van der Aa syndrome

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Loss-function mutations in the ADNP gene are linked to the Helsmoortel-Van der Aa Syndrome (HVDAS), a complex neurological disorder characterized by autism and intellectual disability. Adnp mutant mice recapitulate key hallmark of ASD including learning deficit, increased anxiety and repetitive behavior. ADNP is involved in brain development, neuroprotection and modulation of the immune system. Despite a clear link exists between ADNP and the immune system, to date the exact role of ADNP in immune cell is unknown, and we ignore the contribution of the immune system to the progression or severity of the HVDAS.

A better understanding of the immune changes associated with ADNP deficiency may provide clues to pathological processes and allow to identify biological markers that enable early diagnosis and treatment of ASD. In this project, we will explore the role of ADNP in T cells function, to this end will perform in depth characterization of the molecular and cellular signature acquired by T cells and microglia cell populations in the mutant mice.

Investigating microstructural and histological alterations in a graded contusion rat model of spinal cord injury

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Traumatic spinal cord injury (SCI) is referred to as damage to the spinal cord caused by an external impact resulting in temporary or permanent functional changes and occurs most often at the cervical level of the spinal cord. It can cause paralysis, sensory disturbance, loss of independence, and other clinical manifestations and thus have an enormous impact on the quality of life. Despite the large amount of research that has already been conducted regarding SCI, no treatment options exist to fully restore the injured spinal cord. SCI has a complex pathophysiology where many factors are involved. However, the large heterogeneity in patients with traumatic SCI poses challenges. Experimental animal models can help to study SCI under controlled conditions. The objective of this research aims to microstructurally and histologically characterize graded severity contusion by using a cervical C5 contusion model in rats. The rats were divided into four experimental groups: sham surgery (laminectomy), mild SCI (100 kdyne), moderate SCI (250 kdyne), and severe SCI (400 kdyne) and their spinal cords were collected six weeks after the contusion surgery (chronic phase). Ex vivo diffusion MRI (7T Pharmascan) is used for microstructural characterization, including diffusion tensor imaging (DTI), diffusion kurtosis imaging (DKI), and fixel-based analysis (FBA). For the histological characterization, we are focusing on luxol fast blue (LFB), glial fibrillary acid protein (GFAP), ionized calcium-binding adaptor molecule 1 (Iba1), neurofilament-light (Nf-L) and synaptic vesicle glycoprotein 2A (SV2A). Region-specific analyses within each spinal cord (epicenter, rostral, and caudal of the lesion) will be performed, and outcome will be compared between experimental groups.

Autonomic Nervous System Function and Central Pain Processing in People With Frozen Shoulder. A Case-control Study

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OBJECTIVES: The pathophysiology of a frozen shoulder (FS) is thought to be related to chronic inflammation. Chronic inflammation may disturb the immune system and consequently the nervous system as part of an overarching system. The aim of this study was to determine the presence of disturbed autonomic nervous system function and altered central pain processing (CPP) in patients with FS. Secondarily, the presence of psychological variables (catastrophizing and hypervigilance) and self-reported associated symptoms of altered CPP in patients with FS were investigated.

METHODS: Patients with FS and healthy controls completed the Composite Autonomic Symptom Score (autonomic function) and underwent quantitative sensory testing to assess tactile sensitivity (ie, allodynia), pressure pain thresholds (PPTs, ie, hyperalgesia), temporal summation of pain, and Conditioned Pain Modulation (CPM). Psychological issues were explored with the Pain Catastrophizing Scale and the Pain Vigilance and Awareness Questionnaire, and self-reported symptoms associated with altered CPP were determined with the Central Sensitization Inventory.

RESULTS: Thirty-two patients with FS and 35 healthy controls were analyzed in the study. Patients with FS showed more self-reported autonomic symptoms and symptoms of altered CPP, higher levels of pain catastrophizing and hypervigilance, and are more sensitive to tactile touches and mechanical pressure compared with controls.

DISCUSSION: On the basis of the effect sizes, between-group differences in allodynia, hyperalgesia, catastrophizing, and hypervigilance were clinically relevant, but only local allodynia, hyperalgesia, catastrophizing, and hypervigilance were statistically different. Therefore, obvious altered CPP was not present at the group level in patients with FS compared with controls.

Promising ferroptosis inhibitors to treat Central Nervous System diseases

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Ferroptosis is a mechanism of regulated cell death that plays an important role in various diseases, including central nervous system (CNS) disorders such as Alzheimer's, Parkinson's and amyotrophic lateral sclerosis (ALS). [1] Unlike other types of cell death, ferroptosis is caused by an iron-mediated cell membranes damage making it an important target for potential therapies.

At the Laboratory of Medicinal chemistry and Cell Death Signaling Lab, we focuses on developing small molecules called radical trapping antioxidants, (RTAs) to block ferroptosis. [2] In previous work, we discovered a potent compound UAMC-3203, but its limited ability to cross the blood-brain barrier reduced its effectiveness for treating brain diseases.[3]

To overcome this, we developed new RTAs that can more effectively reach the brain while still blocking ferroptosis. One of these compounds, UAMC-4821, showed great potential in preclinical studies, with strong activity and the ability to reach the brain making it a suitable candidate to treat ferroptosis in neurodegeneration. [4]

Our work contributes to the research of new treatments that can protect the brain from damage and slow the progression of CNS diseases. By refining these compounds, we hope to pave the way for therapies that can target ferroptosis and help improve outcomes for patients suffering from these conditions.

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From noise to neurons: A pilot study investigating the effects of noise-induced hearing loss and noise trauma on cognitive decline in CDH23c.753A>G-corrected C57BL/6N mice

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The link between hearing loss and dementia has emerged as a major public health challenge and has triggered increasing interest with significant opportunities for earlier diagnosis, treatment and prevention. Hearing impairment is one of the most frequent types of sensory deficit, affecting about 20% (or 1.5 billion) of the global population. Regardless of its cause, hearing loss in midlife is considered the primary adjustable risk factor for developing dementia. Currently, more than 55 million people have dementia worldwide, and the World Health Organization predicts that the number of affected individuals will increase to 150 million by 2050. Timely addressing hearing loss could theoretically delay or prevent up to 8% of these dementia cases. Strikingly, despite this crucial clinically established association, the link between the inner ear and cognition remains to be elucidated. Given that high-intensity noise exposure is one of the most common environmental risk factor leading to hearing impairment in midlife, this study investigates the effects of noise-induced hearing loss on cognitive functions using CDH23-corrected C57BL/6N mice. Interestingly, a key question remains whether the observed behavioral and cognitive changes are driven by auditory mechanisms (i.e. structural damage to the inner ear due to noise) or non-auditory mechanisms (noise trauma exposure as a stressful traumatic life event). To differentiate between auditory and noise-stress induced effects, both anesthetized and awake groups of mice are exposed to noise. The severity and timing of cognitive and behavioral parameters are correlated with hearing function, while plasma corticosterone levels serve as a proxy of stress levels. This pilot study allows us to determine whether hearing loss has an additional (and potentially modifiable) impact on cognitive impairment and might provide more insight into the poorly understood mechanisms underlying hearing loss and cognitive decline and dementia.

Longitudinal assessment of changes in the BBB water permeability in a mouse model of Huntington's disease using multi-TE ASL MRI

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Huntington's disease (HD) is a neurodegenerative disorder with neuropsychiatric, cognitive, and motor symptoms, lacking a disease-modifying treatment. It is caused by a mutation in the Huntingtin (HTT) gene, leading to the production of toxic mutant HTT (mHTT) aggregates. Investigating clearance of these aggregates from the brain via the blood-brain barrier (BBB) can potentially lead to the discovery of new biomarkers that can be used to test the efficacy of novel HD treatments. Neuroimaging studies have demonstrated BBB abnormalities in several neurodegenerative disorders, however not yet in HD. We investigated longitudinally the integrity of the BBB water permeability in the zQ175DN HD mouse model using multi-echo time (TE) arterial spin labeling (ASL) MRI, which offers the estimation of blood–tissue water exchange dynamics.

We acquired longitudinal MRI data under isoflurane anesthesia using a 9.4T Biospec MRI scanner in 15 WT and 15 HD zQ175DN mice at 3, 6 and 9 months of age. Within 3 regions of interest, the cerebral blood flow (CBF), arterial transit time (ATT) and the water exchange time were extracted and statistically analyzed using a mixed-effects model.

We observed a progressive reduction in CBF and an increased ATT with age within the somatosensory cortex, independent of genotype. Interestingly, the lack of significant genotype differences in CBF and ATT suggests preservation of the vascular architecture which therefore does not bias the estimation of the water exchange time. Finally, we observed a significantly reduced water exchange time, in both the somatosensory and the cingulate cortex in 9 month old HD mice compared to WT mice.

Due to the absence of significant findings at the younger ages, the multi-TE ASL method may not yield promising biomarkers in this mouse model. However, the results suggests an increased BBB water permeability in cortical regions of the HD mice at 9 months of age that are not caused by changes in the vascular architecture.

Understanding the role of somatic mutations in TARDBP in FTLD-TDP type C

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State of art: Somatic mutations in TARDBP have been reported at the bulk-level in FTLD-TDP type C, a subtype of FTLD characterized by TDP-43 pathology and most often a sporadic occurrence. Systematic identification, replication and validation of somatic TARDBP variants using single-cell methods, however, has not been performed.

Methodology: We performed single-nuclei targeted DNA sequencing of neurons derived from the superior temporal gyrus of FTLD-TDP type C cases (n=53) and controls (n=36) using the Mission Bio Tapestri platform. Samples were pooled in sets of 5. We investigated the somatic variants in TARDBP and compared their burden in a case-control setting.

Results: We first developed a deconvolution strategy leveraging germline variants to assign neuronal nuclei to each individual, resulting in 32,188 nuclei from cases and 5174 nuclei from controls. We identified 2247 somatic TARDBP single nucleotide variants, occurring at a very low frequency and affecting every codon of the gene. Interestingly, we observed a higher burden of non-synonymous TARDBP variants in cases than in controls. Based on careful selection criteria, we also identified non-synonymous variants which are over-represented or exclusively present in cases.

Conclusion: We detected a high level of very rare TARDBP somatic variants in neuronal nuclei in both cases and controls. Our work shows that single nuclei amplicon sequencing offers a novel opportunity to identify rare somatic variants in disease. The identification of variants unique or overrepresented in cases suggests their potential involvement in FTLD-TDP type C, however further analyses and validation is ongoing.

Screen to Cure: SCREEN4PN & MouseKing

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Establishing effective therapies for rare neurological diseases remains one of the greatest challenges in molecular medicine. While advances in AI are accelerating drug discovery, efficient preclinical validation remains a major bottleneck. To address this, we developed a standardized drug screening platform that combines SCREEN4PN, an iPSC-based 2D & 3D cell system assay, and MouseKing, a bioinformatics pipeline for next-generation mouse phenotyping using the Live Mouse Tracker. This unified approach enables robust, scalable assessment of therapeutic efficacy and bridges the gap between drug discovery and translational success in drug development.