

# SWISS DEMENTIA FORUM

**6 – 7 November 2025 | Eventforum**

Abstract Booklet



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## President Welcome

Dear Swiss Dementia Community

It is a great pleasure to welcome you to the first Swiss Dementia Forum in Bern. We have an enriching and interdisciplinary program ahead, thanks to the hard work of our **Scientific Program Chair, Prof. Bogdan Draganski, and his dedicated committee members**. They have brought together leading experts in dementia research from Switzerland and abroad to share their insights.

**Prof. Andreas Papassotiropoulos**, chair of the first keynote and panel discussion, has organized an exciting session featuring three renowned international speakers: **Prof. Charlotte Teunissen, Prof. Frank Jessen, and Dr. Gil Rabinovici**, who will share their different perspectives on early diagnosis, biomarkers and therapy. Joining them are **Dr. Andrea Pfeifer** from AC Immune and **Dr. Tatjana Meyer-Heim**, representing the Swiss Memory Clinics, who will together discuss new horizons in Alzheimer's therapy.

I am particularly looking forward to the evening of Day 1, where attendees can discuss scientific posters while enjoying drinks, followed by an engaging evening program. This will be a fantastic opportunity to connect, network, and exchange ideas.

The second day begins with a distinguished national keynote by **Prof. Marc Aurel Busche**, exploring the underlying mechanisms of dementia. Following another keynote in the afternoon organized by **Dr. Lucie Bréchet** focusing on memory traces. This session will feature three leading experts, **Prof. Katharina Henke, Prof. Johannes Gräff and Dr. Tomas Ryan**, who will offer their insights into the complexities of forgetting.

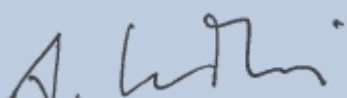
A special feature of our program is the **parallel session format**, which highlights relevant topics in the field, ranging from public health to AI, care aspects, and a session organized in collaboration with the **Swiss Memory Clinics** on blood-based biomarkers. In these parallel sessions, two speakers will present different viewpoints on a shared topic, followed by an interactive discussion led by the chair.

Another highlight are the **lightning sessions**, where 15 selected abstracts will be presented in 6-minute talks, showcasing exciting ongoing projects in the field.

The conference will end with a parallel **workshop session**, offering interactive, hands-on learning opportunities that foster an interdisciplinary dialogue.

I want to finish this letter by highlighting the importance of our sponsors and exhibitors, whose contributions allow us to present this great program at a reasonable cost. We are grateful to all our sponsors for their very important support.

We are looking forward to a productive, inspiring and collaborative two days ahead. Thank you for being a part of this important event. Let us learn, share and work together to advance dementia research and care.



**Prof. Andreas Lüthi,**

President of the Swiss Network for Dementia Research

# Program Overview

## 6 November 2025

02:00 – 03:00 PM	Ground Floor	REGISTRATION AND WELCOME
03:00 – 03:25 PM	Ground Floor	INTRODUCTION OF THE SWISS NETWORK FOR DEMENTIA RESEARCH
03:30 – 05:25 PM	Ground Floor	<b>KEYNOTE &amp; PANEL DISCUSSION: EARLY DIAGNOSIS, BIOMARKERS &amp; THERAPY</b>
05:30 – 08:00 PM	Second Floor	APÉRO & NETWORKING DINNER WITH POSTER SESSIONS
08:00 – 09:00 PM	Ground Floor	EVENING PROGRAM

## 7 November 2025

08:30 – 09:00 AM	Ground Floor	MORNING COFFEE
09:00 – 09:45 AM	Ground Floor	<b>KEYNOTE LECTURE: UNDERLYING MECHANISMS OF DEMENTIA</b>
09:50 – 10:45 AM	Ground Floor	LIGHTNING TALKS
10:45 – 11:15 AM	Second Floor	COFFEE BREAK
11:15 – 12:30 PM	Level – 1 Ground Floor	PARALLEL SESSIONS
12:30 – 02:00 PM	Second Floor	Lunch Break
02:00 – 03:10 PM	Ground Floor	<b>KEYNOTE LECTURES: MEMORY TRACES</b>
03:15 – 04:00 PM	Ground Floor	LIGHTNING TALKS
04:00 – 04:30 PM	Second Floor	COFFEE BREAK
04:30 – 05:40 PM	Level – 1 Ground Floor	PARALLEL WORKSHOP SESSIONS
05:45 – 06:00 PM	Ground Floor	CLOSING PLENARY

# Program Details

## 6 November 2025

**Chair:** Prof. Bogdan Draganski, University of Bern, Board Member of the Swiss Network for Dementia Research and Swiss Memory Clinics

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02:00 – 03:00 PM	Ground Floor	<b>REGISTRATION AND WELCOME</b>
03:00 – 03:25 PM	Ground Floor	<b>INTRODUCTION OF THE SWISS NETWORK FOR DEMENTIA RESEARCH</b>  Dr. Margrit Leuthold, President of Dementia Research Switzerland – Synapsis Foundation  Prof. Bogdan Draganski, Board Member of the Swiss Network for Dementia Research
03:30 – 05:25 PM	Ground Floor	<b>EARLY DIAGNOSIS, BIOMARKERS &amp; THERAPY</b>  <b>Chair:</b> Prof. Andreas Papassotiropoulos, University of Basel  <b>KEYNOTE LECTURES:</b>  <b>Body Fluid Biomarkers in the Era of Alzheimer's Disease Treatment</b> Prof. Charlotte Teunissen, Amsterdam University Medical Center  <b>Stage 2 of Alzheimer's Disease: Evidence and Relevance</b> Prof. Frank Jessen, University of Cologne  <b>Amyloid-Targeting Therapies in Clinical Practice: Lessons from the U.S. Experience</b> Dr. Gil Rabinovici, University of California San Francisco  <b>PANEL DISCUSSION:</b>  <b>New Horizons in Alzheimer's Therapy: Opportunities and Challenges</b>  <b>Panelists:</b> Prof. Charlotte Teunissen, Amsterdam University Medical Center Prof. Frank Jessen, University of Cologne Dr. Gil Rabinovici, University of California San Francisco Dr. Andrea Pfeifer, AC Immune Dr. Tatjana Meyer-Heim, Vice President Swiss Memory Clinics
05:30 – 08:00 PM	Second Floor	<b>APÉRO &amp; NETWORKING DINNER WITH POSTER SESSIONS</b>
08:00 – 09:00 PM	Ground Floor	<b>EVENING PROGRAM</b>  Live music with Skinny Jim Tennessee

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## 7 November 2025

Chair: Prof. Bogdan Draganski, University of Bern, Board Member of the Swiss Network for Dementia Research and Swiss Memory Clinics

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08:30 – 09:00 AM	Ground Floor	<b>MORNING COFFEE</b>
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09:00 – 09:45 AM	Ground Floor	<b>KEYNOTE LECTURE: UNDERLYING MECHANISMS OF DEMENTIA</b> <b>Chair:</b> Prof. Johannes Gräff, EPFL  <b>Early Cellular and Circuit-Level Vulnerabilities in Alzheimer's Disease</b> Prof. Marc Aurel Busche, University of Basel and Universitäre Altersmedizin Felix Platter
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09:50 – 10:45 AM	Ground Floor	<b>LIGHTNING TALKS</b> <b>Chair:</b> Prof. Bogdan Draganski, University of Bern  <b>Clinical Characteristics, Biomarkers, and Prevalence of Cerebral Amyloid Angiopathy in Alzheimer's Disease: Applying the Boston Criteria v2.0 in a Memory Clinic Population</b> Dr. Aurélien Lathulière, University of Geneva  <b>Cerebrospinal Fluid Proteomic Profiles of Depression in Older People in the Context of Cognitive Decline and Alzheimer's Disease</b> Dr. Miriam Rabl, University of Zurich, Psychiatric University Hospital Zurich  <b>Detecting Cognitive Changes Through Continuous Digital Monitoring: Role of AI and Visual Analytics</b> Prof. Arzu Çöltekin, FHNW University of Applied Sciences and Arts Northwestern Switzerland  <b>Suppressing Both Amyloid-β and Tau Is Essential to Restore Neuronal Circuit Function in an Alzheimer's Disease Model</b> Dr. Robert Ellingford, University College London  <b>Characterization of Brain Barrier Fluorescent Reporter Mouse Models of Cerebral Amyloid Angiopathy</b> Linh Tran, Theodor Kocher Institute, University of Bern  <b>Closed-Loop Auditory Stimulation of Deep Sleep Rescues Neuropathological and Phenotypic Hallmarks in Alzheimer's Disease Mice</b> PD Dr. Daniela Noain, University Hospital Zurich  <b>Blarcamesine: A New Oral Treatment Approach for Alzheimer's Disease</b> Prof. Audrey Gabelle, University of Montpellier  <b>Designing Integrated Care Pathways in Ticino and Moesano: Mapping Entry Points and Nodes Through a Participatory Approach</b> Dr. Rebecca Amati, Università della Svizzera italiana
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10:45 – 11:15 AM	Second Floor	<b>COFFEE BREAK</b>
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11:15 – 12:30 PM		<b>PARALLEL SESSIONS</b>
	Level -1 Room 1	<b>BLOOD-BASED BIOMARKERS - SESSION ORGANIZED BY THE SWISS MEMORY CLINICS</b> <b>Chair:</b> Prof. Julius Popp, University of Zurich <b>Monitoring Neurodegeneration through Brain-Derived Extracellular Vesicles in Biofluids</b> Prof. Paolo Arosio, ETH Zurich <b>Blood Based Biomarkers: The HbA1c of Dementia Diagnosis?</b> Dr. Ansgar Felbecker, Inselspital Bern, Praxis St. Gallen
	Level -1 Room 2	<b>AI &amp; DATA ANALYTICS IN DEMENTIA</b> <b>Chair:</b> Prof. Michael Krauthammer, University of Zurich <b>Capturing Cognitive Deficits Through Language Analysis</b> Prof. Philipp Homan, Psychiatric University Hospital Zurich <b>AI-based Voice Assistants for Early Dementia</b> Dr. Rasita Vinay, University of Zurich
	Level -1 Room 3	<b>PUBLIC HEALTH PERSPECTIVES OF DEMENTIA</b> <b>Chair:</b> Prof. Emiliano Albanese, WHO Collaborating Center, University of Geneva and Università della Svizzera italiana <b>Public Policy, Cognitive Health and Dementia: Insights from Natural Experiments</b> Prof. Mauricio Avendano, University of Lausanne <b>Early Detection, Brain Health and Ground-State Prevention: Ethical and Conceptual Challenges for Cognitive Public Health</b> Dr. Alessandro Blasimme, ETH Zurich
	Ground Floor	<b>CARE ASPECTS OF DEMENTIA</b> <b>Chair:</b> Prof. Stefan Klöppel, University of Bern <b>Requirements for Implementing Physical Activation Approaches for People with Dementia in Care Homes to Maintain Their Everyday Abilities</b> Prof. Steffen Heinrich, Ostschweizer Fachhochschule <b>Care for People with Dementia in Swiss Nursing Homes: Legal and Financial Framework and the Diversity of Practice</b> Dr. Christina Zweifel, CURAVIVA
12:30 – 02:00 PM	Second Floor	<b>LUNCH BREAK</b>
02.00 – 03.10 PM	Ground Floor	<b>KEYNOTE LECTURES: MEMORY TRACES</b> <b>Chair:</b> Dr. Lucie Bréchet, University of Geneva <b>Unconscious Episodic Memory Despite Severe Memory Impairment?</b> Prof. Katharina Henke, University of Bern  <b>Memory Traces on the Chromatin</b> Prof. Johannes Gräff, EPFL  <b>Forgetting as a Form of Learning</b> Dr. Tomas Ryan, Trinity College Dublin, Ireland

03:15 – 04:00 PM	Ground Floor	<p><b>LIGHTNING TALKS</b></p> <p><b>Chair:</b> Prof. Bogdan Draganski, University of Bern</p> <p><b>Elucidation of Amyloid-Beta’s Gambit in Oligomerization</b> Dr. Adrien Schmid, EPFL</p> <p><b>Therapeutic Potential of Mitochondrial Transplantation in a Cellular Model of Tauopathy</b> Aline Broeglin, University of Basel</p> <p><b>Biological Characterization of Frontotemporal Dementia (FTD) Using Human Induced Pluripotent Stem Cells (hiPSCs): An Innovative Approach of the Swiss FTD Network</b> Dr. Paolo Salvioni Chiabotti, Leenaards Memory Center, University of Lausanne</p> <p><b>Uncoupling Between Tau Deposition and Hypometabolism in the Brain Explains Heterogeneity in Alzheimer’s Disease</b> Dr. Cecilia Boccalini, University of Geneva</p> <p><b>Slow Wave–Spindle Coupling During Deep Sleep Is Uniquely Linked to Plasma Amyloid-β Levels in Older Adults</b> Dr. Marina Wunderlin, University Hospital of Old Age Psychiatry and Psychotherapy</p> <p><b>Memories Fade, Traces Remain: Neural and Behavioural Correlates of Forgotten Episodic Memories Found After 6 Months With 7T fMRI</b> Konstantinos Ioannis Zervas, University of Bern</p> <p><b>Preliminary Data on Power Spectral Analysis of Resting-State EEG in Cognitive Decline and Healthy Aging</b> Camille Bouhour, University of Geneva</p>
04:00 – 04:30 PM	Second Floor	<b>COFFEE BREAK</b>
04:30 – 05:40 PM		<b>PARALLEL WORKSHOP SESSIONS</b>
	Level -1 Room 1	<p><b>Producing Useful Evidence – Translation Methodology for Implementation</b> Prof. Marina Boccardi, University of Applied Sciences of Southern Switzerland</p>
	Level -1 Room 2	<p><b>A Case Study in Translation: From Research Data to a Start-up for a New Dementia Therapy</b> Dr. Stéphane Pagès, Wyss Center</p>
	Level -1 Room 3	<p><b>Success Factors for Interdisciplinary Collaboration in Dementia Research</b> Dr. Kevin Richetin, Leenaards Memory Center and Center of Psychiatric Neurosciences, CHUV</p>
	Ground Floor	<p><b>Developing Patient Centered and Ethical Dementia Research</b> Dr. Kelly Ormond, ETH Zurich</p>
05:45 – 06:00 PM	Ground Floor	<b>CLOSING PLENARY &amp; AWARD CEREMONY</b>

## Scientific Committee

Chaired by **Prof. Bogdan Draganski** (University of Bern), the organizing committee is the driving force behind the program, carefully selecting topics, shaping the agenda and inviting distinguished speakers.

What makes this committee unique is its diverse expertise, uniting leading and emerging researchers from fields such as biomarkers, epidemiology, machine learning, memory research, cognition, and aging. This interdisciplinary approach is intentional, ensuring a broad and inclusive perspective. By prioritizing both regional and cross-disciplinary insights, the committee strives to present a comprehensive and dynamic overview of dementia research in Switzerland.



**Prof. Emiliano Albanese**

WHO Collaborating Center,  
University of Geneva and  
Università della Svizzera italiana



**Prof. Gilles Allali**

University of Lausanne



**Dr. Lucie Bréchet**

University of  
Geneva



**Prof. Katharina Henke**

University of Berne



**Prof. Michael  
Krauthammer**

University of Zurich



**Prof. Andreas  
Papassotiropoulos**

University of Basel

# **Keynote Lectures**

## K1-01: Body Fluid Biomarkers in the Era of Treatment of Alzheimer's Disease

**Prof. Charlotte Teunissen, Amsterdam University Medical Center**

Plasma biomarkers for Alzheimer's disease (AD) are promising tools due to their high accuracy and application ease. They can fill an important need in the current era of application of disease modifying therapies and boost in therapy development.

In this latter context, development and validation of fluid biomarkers are getting more and more important. They are crucial as objective outcome measures of clinical trials, yet more biomarkers need to be developed: we observed in a systematic analysis that only one-third of the recently conducted clinical trials for Alzheimer's disease applied fluid biomarkers as outcomes.

I will discuss the road towards swift development of fluid biomarkers for diagnostic, prognostic, prediction of response to therapy, monitoring therapeutic responses and safety (e.g. to predict and monitor ARIA) fluid biomarkers, and show new data for all these purposes in drug development programs. Next, biomarkers are needed for multiple causes of dementia. Among the highlights is the biomarker development of CSF dopamine decarboxylase for dementia with Lewy bodies. In this increasing wealth of measurement options, education and interpretation support tools are needed. All these efforts will ultimately lead to a rich armory to improve treatment and care of patients with dementia.



## K1-02: Stage 2 of Alzheimer's Disease: Evidence and Relevance

**Prof. Frank Jessen, University of Cologne**

The first generation of causal treatments open the door towards effective slowing of Alzheimer's disease (AD) progression. In this regard, current data suggest that early treatment is more effective than treatment initiation at later disease stages. The amyloid-targeting antibodies lecanemab and donanemab are approved for early AD, which comprises the stage of mild cognitive impairment (MCI) and mild dementia. These conditions correspond to the symptomatic stage 3 and 4 of the criteria of the Alzheimer's Association (AA). First symptoms, however, occur already at stage 2 of AD. According to the AA criteria, the symptoms of stage 2 are subjective cognitive decline (SCD), subtle objective decline and mild behavioural symptoms, either individually or in combination. Traditionally, stage 2 of AD is combined with the fully asymptomatic stage 1 to preclinical AD, and current secondary prevention trials with amyloid-targeting antibodies focus on the combined condition of stage 1 and stage 2. In the presentation, data mainly of the German DELCODE study will be presented, which demonstrate the difference of stage 1 and stage 2 not only regarding the absence or presence of symptoms, but also regarding disease progression. Consequences for the designs of secondary prevention trials, but also the potential value of a clinical conceptualization of stage 2 will be discussed.



## K1-03: Amyloid-Targeting Therapies in Clinical Practice: Lessons from the U.S. Experience

**Dr. Gil Rabinovici, University of California San Francisco**

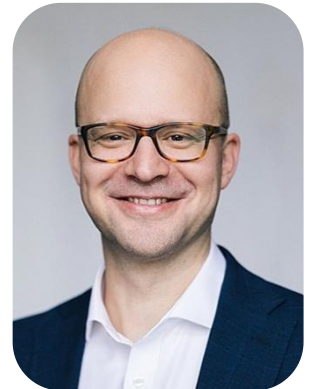
In July 2023, the U.S. Food & Drug Administration (FDA) granted full approval to lecanemab for the treatment of early clinical Alzheimer's disease (AD), followed one year later by full approval of donanemab for the same clinical indication. FDA approval paved the road for insurance reimbursement by the Centers for Medicare and Medicaid Services and private third-party payers. Overall, amyloid-targeting therapies have led to a sea change in clinical workflows for the diagnosis and management of AD, leading to widespread clinical use of biomarkers and requiring close multidisciplinary collaborations across neurology specialties and between neurology and other medical departments (e.g. Radiology, Nuclear Medicine Emergency Medicine). In this lecture I will provide lessons learned from our experience implementing these therapies in the U.S. I will describe in detail the resources and systems we developed in our large academic memory clinic for safe and effective delivery of these therapies, showcase initial data from our center and others regarding the treated population and safety outcomes, and discuss national and global efforts to capture real-world data on the safety and efficacy of amyloid-targeting therapies and future novel drugs for AD and related dementias.



## K2-01: Early Cellular and Circuit-Level Vulnerabilities in Alzheimer's Disease

**Prof. Marc Aurel Busche, University of Basel and Universitäre Altersmedizin Felix Platter**

A key challenge in Alzheimer's disease (AD) is to understand why certain brain cell types and circuits are especially vulnerable, while others remain resilient. Defining the mechanisms underlying this selective vulnerability is critical for developing effective, mechanism-based therapies and early diagnostic markers. In this talk, I will present recent findings from our work using brain-wide imaging and in vivo electrophysiology to uncover how amyloid-beta and tau - the two key pathological proteins in AD - impair circuit function across different brain regions, timescales, and cell types. We discovered that oligodendrocytes, not only neurons, are a major source of soluble amyloid-beta in the diseased brain, challenging conventional neuron-centric models. I will also highlight the earliest impairments in cortical function caused by amyloid-beta accumulation, and the distinct, cell-type-specific mechanisms involved. Furthermore, I will discuss how high-molecular-weight soluble tau affects hippocampal neuron excitability and computation, and how these early changes may represent critical tipping points in disease progression, before dysfunction becomes irreversible. By defining these early tipping points, we aim to build a mechanistic framework linking molecular pathology to circuit dysfunction and the emergence of both cognitive and non-cognitive symptoms in AD. Understanding the temporal trajectory of these changes may help identify optimal windows for therapeutic intervention, before irreversible damage takes hold.



## K3-01: Unconscious Episodic Memory Despite Severe Memory Impairment

**Prof. Katharina Henke, University of Bern**

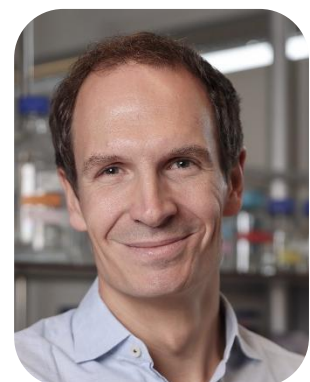
A common view is that forgetting is due to the dissipation of the neural memory traces (engrams). Recent engram research in mice, however, suggests that the engrams of forgotten memories persist. This raises the question whether engrams underlying human episodic memories also persist despite forgetting in healthy people and in amnesic patients? If engrams persist, do forgotten memories continue to influence human behavior? Using high-resolution functional magnetic resonance imaging at 7 Tesla we mapped the fate of 96 newly formed relational memories at the systems level from learning to a 30-minute retrieval, to a 24-hour retrieval, to a one-week retrieval, and to a six-month retrieval in healthy participants. Upon each retrieval attempt, participants indicated whether they remembered or forgot the memory. Univariate and multivariate analyses of the functional brain data revealed that the engrams of forgotten memories remain implemented in the episodic memory network including the hippocampus and continue to influence the accuracy of guessing responses at test. Even amnesic patients performed normally on a relational encoding and retrieval task despite amnesia capitalizing on spared hippocampal tissue and connections to language cortex. Although their retrieval was unconscious and therefore consisted in guessing, the accuracy of guessing was above chance level. This is evidence that forgotten episodic memories may remain implemented in the episodic memory network and continue to influence our behavior. Contrary to what traditional memory models claim, episodic memories may therefore exist with and without being consciously accessible.



## K3-02: Memory Traces on the Chromatin

**Prof. Johannes Gräff, EPFL**

Memory formation relies on a bidirectional interplay between synaptic plasticity and nucleus-templated transcriptional programs, but how precisely this interplay is orchestrated by epigenetic mechanisms remains to a large extent unknown. In this talk, I will showcase our recent efforts to better understand this aspect from two angles. First, we have found that chromatin plasticity in the mouse brain is a key determinant for memory allocation, the process by which neurons become recruited into the memory trace. Second, we have found that after encoding, the epigenetic editing of a single locus in the encoding ensemble can bidirectionally alter memory performance across different phases of memory consolidation. Together, these findings stipulate that before and after memory encoding, epigenetic mechanisms play a pivotal role as molecular memory aids.



## K3-03: Forgetting as a Form of Learning

**Dr. Tomas Ryan, Trinity College Dublin**

'Forgetting' generally refers to the loss of previously formed memories. Although multiple forms of forgetting have been characterized, ranging from natural "every day" forgetting to unnatural pathological forgetting, a formal scientific framework with which to explain and investigate the neuroscience of forgetting is lacking. Forgetting has been regarded as a defect of the brain, but contemporary research is challenging this paradigm. An alternative perspective has emerged where forgetting may be viewed as an adaptive feature of the brain that allows an organism to respond optimally to its environment.

In my lecture, I will summarize behavioural studies that imply that forgetting serves adaptive functions to allow organisms to generalize and abstract from initial experiences. I will discuss a growing body of findings that demonstrate that forgetting is based on active neurobiological mechanisms that respond to environmental experience. I will introduce "engram cell labelling" methodologies, which allows us to genetically label, observe, and manipulate the specific ensembles of neurons that encode particular memories in the rodent brain. I will show how many forms of forgetting are in fact reversible, and that the core information endures within the brain's engrams. Finally, I will outline a novel framework that considers both natural and unnatural forgetting to be predictive processes that involve the interaction of a subject's priors with perceptual experience.



# **Panel Discussion**

## PD-01: New Horizons in Alzheimer's Therapy - Opportunities and Challenges

Chair: Prof. Andreas Papassotiropoulos, University of Basel

Panelists:

Prof. Charlotte Teunissen, Amsterdam University Medical Center

Prof. Frank Jessen, University of Cologne

Dr. Gil Rabinovici, University of California San Francisco

Dr. Andrea Pfeifer, CEO AC Immune

Dr. Tatjana Meyer-Heim, Vice President Swiss Memory Clinic

Following the keynote lectures by Prof. Charlotte Teunissen, Prof. Frank Jessen, and Dr. Gil Rabinovici, each offering a distinct perspective on biomarkers, early intervention, and the clinical implementation of novel Alzheimer's therapies, this panel discussion will broaden the conversation to include insights from across the Alzheimer's field.

Joining the keynote speakers, Dr. Andrea Pfeifer, CEO of AC Immune, will provide the industry perspective on translating scientific discoveries into safe and effective treatments. Tatjana Meyer-Heim, vice president of the Swiss Memory Clinics, will contribute insights from daily clinical practice, including the readiness of healthcare systems to deliver these emerging therapies.

Together, the panelists will explore opportunities and challenges in advancing Alzheimer's therapies, spanning biomarker-based blood tests for early detection, anti-amyloid antibody treatments, and the practical aspects of integrating these innovations into clinical practice. This discussion is particularly timely, as Lecanemab is expected to gain Swissmedic approval, potentially becoming the first monoclonal antibody treatment for Alzheimer's authorised in Switzerland. Although anti- $\beta$ -amyloid monoclonal antibodies received earlier approval in the US in 2023, their clinical impact remains debated. Some experts emphasize their disease-modifying potential, while others question the benefit-to-risk ratio.

The panel will critically examine the balance between optimism and caution: What is the true clinical value of these emerging treatments? And what alternative or complementary strategies may hold promise in the broader effort to combat Alzheimer's disease?

# Parallel Sessions

## **P1: Blood-based biomarkers – session organized by the Swiss Memory Clinics**

**Chair: Prof. Julius Popp, University of Zurich**

Important steps forwards have been made in recent years to discover new biomarkers, develop easy- to-use technologies, and validate these markers for clinical use. The new blood-based biomarkers represent the most important progress, promising to radically change the way we diagnose neurodegenerative diseases, assess disease progression, and monitor the effects of disease-modifying drugs. In this symposium organized by Swiss Memory Clinics, Prof. P. Arosio will present perspectives and challenges in biomarker discovery using brain-derived extracellular vesicles. The second talk by Dr. A. Felbecker will focus on the clinical research on blood-based biomarkers and the progress made towards clinical use.

### **P1-01: Monitoring neurodegeneration through brain-derived extracellular vesicles in biofluids**

**Prof. Paolo Arosio, ETH Zurich**

The identification of neurodegenerative disease biomarkers in easily accessible body fluids is crucial in the fight against this class of disorders. Brain-derived extracellular vesicles (EVs) have gained attention as nanoscale carriers of molecular information and bioactive molecules that reflect the status of their source cells. By crossing the blood-brain barrier, EVs can transfer these biomolecular signatures to peripheral biofluids, setting the scene for their use as biomarkers. However, a key obstacle in leveraging EVs for liquid biopsy is their challenging isolation from complex biofluids. This presentation will highlight our recent advancements in developing technologies to streamline EV isolation and characterization, thus enhancing the information content obtained from these biological nanoparticles.

### **P1-02: Blood based biomarkers: the HbA1c of dementia diagnosis?**

**Dr. Ansgar Felbecker, Inselspital Bern, Neurologische Praxis St. Gallen**

Emerging treatments in the field of dementia require earlier and more precise diagnosis, as they target specific pathologies. Traditional biomarkers in cerebrospinal fluid (CSF) or with PET technologies are either expensive, not broadly available and/or invasive.

Blood based biomarkers (BBB) aim to fill this gap: they should be easily accessible, cheaper and at least as precise as the former standard of care (CSF biomarkers). While research in this field has moved forward in a tremendous speed during the last years, BBB are still not available in clinical routine in most places.

The talk will give an overview on the current state of the clinical research on BBB in the field of dementia. We will discuss the research methods, results, and limitations of BBB so far, especially regarding the future implementation and clinical use.

Furthermore, there is an urgent need for more research in this field: the story is not over once BBB for early diagnosis of Alzheimer's disease are established. We will also discuss future research directions, with science moving to new challenges like other neurodegenerative diseases, more precise definition of disease stages and monitoring of new treatments. In other words: BBB might be a key to personalized medicine in the future.

## P2: AI & data analytics in dementia

**Chair: Prof. Michael Krauthammer, University of Zurich**

This session explores the potential of artificial intelligence and data analytics to change dementia research, diagnosis, and care. Prof. Philipp Homan will present on the use of speech and language analysis as biomarkers for cognitive deficits, providing new approaches to diagnosis, prognosis, and simulation-based medicine. Dr. Rasita Vinay will introduce GRACE, an LLM-based voice assistant that supports autonomy in early dementia and reduces caregiver burden. The session will also examine ethical, social, and security considerations, including privacy, consent, and responsible use of data, showing how AI can both enable and challenge the future of dementia care.

### P2-01: Capturing cognitive deficits through language analysis

**Prof. Philipp Homan, Psychiatric University Hospital Zurich**

Language is increasingly viewed as a suitable readout of cognition, reflecting how knowledge is accessed, choices are made, and attention is directed. In dementia, these processes deteriorate in distinct and gradual ways. Spoken responses can therefore be treated not merely as counts or errors, but as structured behavioral data that allow cognitive change to be modeled over time. Short and repeatable tasks, such as category fluency or brief narratives, can yield word sequences that contain information about search efficiency, semantic organization, and stopping behavior. Through AI-based modeling, these sequences can be reduced to a small set of stable indicators that capture how information is retrieved, switched, and exhausted, and that can be compared within person across repeated assessments rather than only against population norms. The potential value for dementia research and care lies in longitudinal precision. Signals can be obtained at clinic visits or in naturalistic settings, with minimal burden. Because the indicators describe behavior rather than only summarize it, they tend to be less affected by transient variability and more sensitive to gradual decline. When combined with demographic and biological data, they may support refined prognosis and individualized monitoring of cognitive trajectories.

### P2-02: AI-based voice assistants for early dementia

**Dr. Rasita Vinay, University of Zurich**

Artificial intelligence (AI) is rapidly transforming dementia care, offering new opportunities but also raising profound challenges. This presentation introduces the LLM-based voice assistant, GRACE, and results from its pilot studies, which investigate the feasibility and acceptance of conversational AI to support people with early dementia. However, deploying AI in sensitive health contexts requires rigorous ethical reflection. Key issues include data privacy, ensuring meaningful consent in populations with cognitive decline, and establishing trustworthiness in systems that mediate care. These considerations are central to ensuring responsible adoption of AI systems in care settings. To address certain ethical and regulatory concerns, the role of simulated data, such as AI personas, must also be considered for advancing dementia research and care. These methods hold promise for training, testing, and scaling interventions without relying exclusively on patient data. At the same time, they raise important questions about authenticity, representation, and the future of evidence in medicine. By weaving together pilot study results, ethical considerations and methodological innovation, this presentation will highlight how AI and data analytics can both enable and challenge the future of dementia care.

## **P3: Public health perspectives of dementia**

**Chair: Prof. Emiliano Albanese, WHO Collaborating Center, University of Geneva and Università della Svizzera italiana**

This parallel session focuses on how different disciplines and perspectives can contribute to an effective and efficient collaborative environment aimed at reducing the burden of dementia. Prof. Mauricio Avendano will present from a public health and policy perspective while Dr. Alessandro Blasimme will add the ethical and philosophical view. In light of these two presentations, we will discuss how different approaches including basic to clinical science can foster convergence to advance knowledge, strengthen the evidence base, and inform action.

### **P3-01: Public policy, cognitive health and dementia: Insights from natural experiments**

**Prof. Mauricio Avendano, University of Lausanne**

Investments in Dementia research have primarily focused on individual-level treatment and targeted prevention approaches, with comparatively little attention to public health approaches that aim to reduce risk through population-wide policies. In this presentation, I argue for the importance of complementing individual-level approaches with population-based strategies, introducing the concept of the policy exposome as a framework to achieve this. Although several modifiable risk factors for Dementia have been identified, little is known about how public policies that shape these risk factors shape the risk of Dementia across populations. I propose the development of research infrastructures that enable studying the impact of public policies on dementia worldwide. The policy exposome seeks to capture the cumulative policies environment to which individuals are exposed to across the life-course, potentially affecting cognitive function and dementia risk. To illustrate this approach, I discuss evidence linking education and public transportation policies to cognitive outcomes in later life. The presentation concludes with findings from a recent expert and stakeholder survey identifying key priorities for advancing research on policy determinants of dementia.

### **P3-02: Early detection, brain health and ground-state prevention: Ethical and conceptual challenges for cognitive public health**

**Dr. Alessandro Blasimme, ETH Zurich**

Efforts to promote brain health increasingly emphasize early detection and preventive strategies aimed at preserving cognitive function and bolster cognitive reserve. While these approaches promise to delay or avert neurodegenerative diseases, they also raise complex ethical and conceptual questions. The extension of a preventive logic into the pre-clinical sphere is not unique to brain health. Healthy aging is premised on targeting common risk factors for a variety age-related disorders undermining functioning and autonomy. I have called this approach to prevention, ground-state prevention. Ground-state prevention redefines what it means to be healthy, transforming citizens into subjects of novel forms of self-surveillance, self-care and health promotion. Early detection technologies - including digital health technologies and associated AI models - blur the boundaries between health and disease, risk and pathology, and care and control. This anticipatory model of brain health governance reconfigures moral responsibility, promoting ideals of vigilance and self-optimization that yet need to come into alignment with social solidarity and health equity. This talk looks at early detection in brain health through the lenses of ground-state prevention, calling for a re-examination of what it means to protect brain health ethically in an age of prediction.

## **P4: Care aspects of dementia**

**Chair: Prof. Stefan Klöppel, University of Bern**

This session examines how structural, organizational, and financial factors influence the quality of dementia care in Swiss nursing homes. Prof. Steffen Heinrich (Ostschweizer Fachhochschule) will focus on one key quality dimension, activity, discussing strategies to reduce residents' high levels of inactivity by integrating physical activation into daily care routines. His talk highlights the ViSTA program, a simple, person-centered activation approach, and the key factors that support its successful implementation. Dr. Christina Zweifel (CURAVIVA) will explore the legal and financial frameworks shaping dementia care, including cantonal diversity, upcoming EFAS reforms, and their practical impact. The session invites discussion on how to ensure equitable, person-centered dementia care and how policy reforms can support institutions in maintaining high-quality care.

### **P4-01: Requirements for implementing physical activation approaches for people with dementia in care homes to maintain their everyday abilities**

**Prof. Steffen Heinrich, Ostschweizer Fachhochschule**

Person-centered care and activation are crucial for maintaining quality of life and daily living skills (ADL) in people with dementia. However, their implementation in long-term care is often challenged by structural barriers such as limited staff resources, time constraints, and varying levels of motivation among both residents and caregivers. Identifying and shaping the necessary framework conditions is therefore essential for sustainable practice change.

This presentation will highlight key determinants that enable person-centered activation in nursing home settings, including organizational structures, team processes, staff training, and the integration of activation into everyday routines. A central focus will be the ViSTA program (Vitalizing Training Program for Seniors in Long-Term Care Institutions), which was developed through a systematic review of implementation determinants of existing activation programs and refined by a multi-professional expert panel. ViSTA combines low-threshold physical activation with playful elements, exergaming, and visual feedback to foster empowerment and independence among seniors with and without dementia.

Findings from the pilot phase indicate good feasibility, high acceptance, and positive motivational effects, while also reducing the burden on care staff. Under appropriate organizational and structural conditions, ViSTA offers a promising approach to preserve daily living skills and enhance the satisfaction with the care environment for people with and without dementia in long-term care settings.

### **P4-02: Care for people with dementia in Swiss nursing homes: Legal and financial framework and the diversity of practices**

**Dr. Christina Zweifel, CURAVIVA**

Care for people with dementia in Swiss nursing homes takes place within a complex legal and financial framework that reflects both federal principles and strong cantonal diversity. The presentation explores how these frameworks shape daily practice, quality of care, and residents' rights. The legal dimension is defined by the interplay between health and social care legislation, capacity and consent regulations, and protective measures under civil law. Financially, ongoing reforms – notably the upcoming EFAS (Einheitliche Finanzierung von ambulant und stationär) – aim to harmonise the funding of long-term care but raise key questions for the sustainability of dementia

care in residential settings. The presentation highlights the diversity of practice across Switzerland, influenced by varying cantonal financing models, organisational cultures, and staffing structures. Examples from member institutions illustrate innovative approaches to balancing autonomy, safety, and participation for residents with cognitive impairments. By connecting the legal, financial, and practical perspectives, the presentation invites discussion on how to ensure equitable, person-centered dementia care across all regions – and how policy reforms can support institutions in maintaining quality and dignity in a changing environment.

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Alzheimer's disease and other dementias are the seventh leading cause of death worldwide and one of the major causes of disability and dependency among older people globally. In 2023, it was estimated that over 55 million people worldwide were living with dementia – a figure projected to triple to 150 million by 2050. With more than two decades of scientific research in Alzheimer's, Roche is working together with our partners, towards a day when we can detect and treat the disease early enough to slow down, stop or even prevent its progression and preserve what makes people who they are. We are committed to developing diagnostic and therapeutic treatments across the full spectrum of the disease pathway - from timely detection and diagnosis to treatment and ongoing monitoring of the disease. We understand that the pathophysiology of AD is complex and multiple mechanisms may be involved in the pathology. Therefore, in parallel to amyloid targeting therapies such as trontinemab (Phase III) and nivegaceter (Phase II), we are assessing the potential of multiple targets involved in the disease pathogenesis so we can tackle this complex disease from different angles and find solutions faster for people with Alzheimer's.



# Workshops

## W1: Producing useful evidence – translation methodology for implementation

**Prof. Marina Boccardi, University of Applied Sciences of Southern Switzerland**

We distinguish translational research and innovation adoption as separate chapters. However, they are part of a continuous, more similar to the technological R&D pipeline than to basic science. How can we connect them to benefit our everyday work?

We will start from a presentation of a template methodology, and will apply that framework to specific use cases. Depending on the number and interests of participants, they can work collectively or within separate subgroups, to actively find out which are the sequential steps connecting theory/research to practice in specific areas, to achieve effective implementation and societal impact. They will be prompted to ask the key questions needed to proceed, to involve the relevant stakeholders required to inform specific development steps, and to use available tools.

Use-cases may include both biomedical research and non-pharmacological intervention, to illustrate how the same logics applies.

## W2: A case study in translation: from research data to a start-up for a new dementia therapy

**Dr. Stéphane Pagès, Wyss Center**

Translating promising research findings into impactful therapies is a complex and multidisciplinary journey. This interactive workshop will guide participants through the critical steps of transforming an idea at the lab bench into a viable start-up dedicated to advancing a new dementia therapy. Using a case study format, we will explore the translation pathway from scientific discovery to clinical and market readiness.

Key aspects will include identifying and validating unmet medical needs, shaping a robust intellectual property (IP) and regulatory strategy, and building an effective business model that attracts investors and partners. Participants will gain insights into the unique challenges of developing dementia-focused therapies, where scientific, ethical, and practical considerations intersect. We will highlight decision points, potential pitfalls, and enabling factors, drawing on real-world experiences to illustrate best practices.

By the end of the session, attendees will better understand how to navigate the translational process, foster collaborations, and position innovations for long-term success. The workshop aims to empower researchers, clinicians, entrepreneurs, and policymakers with actionable knowledge to accelerate the delivery of new solutions for people living with dementia.

## **W3: Success factors for interdisciplinary collaboration in dementia research**

**Dr. Kevin Richetin, Leenaards Memory Center and Center of Psychiatric Neurosciences, CHUV**

Effective interdisciplinary collaboration is essential to advance dementia research, yet projects often face challenges linked to differing professional cultures, expectations, and timelines. This workshop explores concrete success factors that allow collaborations to thrive from project launch to translation into practice. Following a short introduction, a live poll will map participants' profiles and motivations. In mixed working groups, participants will work through scenarios that highlight common obstacles—such as misaligned agendas, communication gaps, or unclear governance—and identify practical strategies to overcome them. A plenary discussion will synthesize these insights, leading to a shared set of success factors and actionable recommendations. The workshop concludes with examples of institutional initiatives supporting collaboration, ensuring that attendees leave with both conceptual frameworks and practical tools to strengthen interdisciplinary dementia research.

## **W4: Developing patient centered and ethical dementia research**

**Dr. Kelly Ormond, ETH Zurich**

In this workshop, we will use an interactive approach to discuss ethical issues that arise in all phases of dementia research, including study methodology, planning, recruitment, data collection and return of results. We will also discuss the importance of including PPI advisors at all stages of the project and ways to do so. Finally, we will use small group case discussions among participants to work through real-life scenarios. If participants bring their own research examples of ethical challenges, these can also be discussed. Helpful resources will be included.

# Lightning Talks

Friday, 7 November 2025 | 09:50 – 10:45 AM

## L1-01: Clinical characteristics, biomarkers and prevalence of cerebral amyloid angiopathy in Alzheimer's disease: Applying the Boston criteria v2.0 in a memory clinic population

Hadrien M. Lalive<sup>1</sup>, Federica Ribaldi<sup>1,2</sup>, Augusto J Mendes<sup>1,2</sup>, Chen Wang<sup>1</sup>, Christian Chicherio<sup>1,3</sup>, Max Scheffler<sup>4</sup>, Karl Olof Lövblad<sup>5</sup>, Giovanni B Frisoni<sup>1</sup>, **Aurélien Lathuilière<sup>1</sup>**

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<sup>3</sup> Center for Interdisciplinary Study of Gerontology and Vulnerability (CIGEV), University of Geneva, Geneva, Switzerland.

<sup>4</sup> Division of Radiology, Geneva University Hospitals, Geneva, Switzerland

<sup>5</sup> Division of Neuroradiology, Geneva University Hospitals, Geneva, Switzerland.

Background: CAA diagnosis has become more important with the advent of anti-amyloid therapies, given its association with amyloid-related imaging abnormalities. While the Boston criteria are widely used in memory clinics, the prevalence and clinical correlates of CAA in biomarker-confirmed AD remain unclear.

Objective: To determine the prevalence of cerebral amyloid angiopathy (CAA) in cognitively impaired older adults with biomarker-confirmed Alzheimer's disease (CI-AD) using the Boston criteria v.2.0, and to compare clinical, cognitive, and biomarker profiles between CI-AD patients with and without CAA.

Methods: We retrospectively identified 506 patients with probable AD, confirmed by cerebrospinal fluid (CSF) or positron emission tomography (PET) biomarkers, from the Geneva University Hospitals Memory Center database (2012 – 2024). MRI scans were evaluated by a radiologist or neuroradiologist, independently reviewed by a blinded analyst, and diagnoses confirmed by a neurologist. Patients were classified as high (AD-CAA) or low probability of CAA (AD-nCAA) using the Boston criteria v.2.0. Clinical, cognitive, and biomarker profiles were compared using the Chi-squared test or Fisher's exact test for categorical variables and the Mann-Whitney U test for continuous variables. Longitudinal cognitive decline was assessed using a linear mixed-effects model.

Results: 29% (n = 146) of CI-AD patients had a high risk of CAA. Compared to AD-nCAA, AD-CAA patients were older, more frequently on antiplatelet therapy, and had greater cerebrovascular comorbidity, despite similar vascular risk. No group differences were observed in CSF/PET biomarkers or medial temporal atrophy. Baseline cognition, including memory and executive functions, was comparable. MMSE declined by 0.10 points/month (95% CI: -0.12 to -0.08, p<.001), with no difference in decline between groups (p=.886).

Conclusion: Nearly one-third of CI-AD patients had high risk of CAA, lower than pathology-based estimates. CAA status was not associated with biomarker burden or cognitive decline, highlighting the need for further research into its clinical implications in memory clinic populations; and questioning the use of the Boston criteria v.2.0 in AD.

## L1-02: Cerebrospinal fluid proteomic profiles of depression in older people in the context of cognitive decline and Alzheimer's disease

Miriam Rabl, Julius Popp

University of Zurich

**Introduction:** Depressive symptoms are common in older people with cognitive decline and Alzheimer's disease (AD), may occur at early stages, and contribute to clinical progression. Little is known about the underlying pathology. Here, we applied untargeted proteomics in cerebrospinal fluid (CSF) to investigate CNS biological pathway alterations related to depression in cognitive decline and AD.

**Methods:** We considered individuals with normal cognition (NC), mild cognitive impairment (MCI), or mild AD dementia from the Amsterdam Dementia Cohort (ADC) and the multi-centre European Medical Information Framework for AD Multimodal Biomarker Discovery study (EMIF-AD). Depressive symptoms were assessed using the Geriatric Depression Scale (GDS). Untargeted CSF proteomics was performed using mass spectrometry. Linear regression was applied to identify proteomic associations with GDS scores in both cohorts. Pathway enrichment analysis was performed using the gene ontology and KEGG databases. Interaction terms were included to test if associations between protein levels and GDS scores were dependent on amyloid status.

**Results:** A total of 688 individuals (223 with NC, 190 with MCI, 275 with AD dementia) were included. The CSF levels of 57 out of 946 proteins were associated with depression scores, with 48 proteins upregulated and 8 downregulated consistently across both cohorts. Pathway enrichment analysis indicated involvement of proteins related to cell adhesion/inflammation, synaptic signaling, and neurogenesis. When considering only subjects with cerebral amyloid pathology additional proteins were found to be related to depression scores. Most of these proteins were involved in the lipid metabolism, in particular in the cholesterol transport and metabolism.

**Conclusion:** Using untargeted CSF proteomics in two AD cohorts, we identified distinct pathway alterations related to depression symptoms, with specific alterations observed in participants in the AD continuum. The results suggest distinct pathomechanisms underlying depression symptoms, which may represent intervention targets to treat depression in cognitive decline and AD.

## L1-03: Detecting cognitive changes through continuous digital monitoring: Role of AI and visual analytics

Arzu Çöltekin

Institute of Interactive Technologies, School of Computer Science, FHNW University of Applied Sciences and Arts Northwestern Switzerland

Recent developments in computer- and data science domains, specifically the lean applications that can run on mobile devices such as mobile phones and tablets, new artificial intelligence (machine- and deep learning) paradigms, and a new appreciation of designing systems that enable human-AI collaborations offer exciting possibilities also in the world of dementia prediction, monitoring and possibly interventions.

In this talk, we offer insights from two efforts: One is from cognitive data obtained through a mobile app that is re-envisioned cognitive testing augmented reality (AR) and other gamified feature (the Altoida App). Our studies reveal that the app picks up signs of conversion from mild cognitive impairment (MCI) to Alzheimer's Disease (AD), and cognitive improvements observed in cardiac patients after a surgery, both of which demonstrate evidence that continuous monitoring is possible and offers unique insights. The second effort is an exploratory study on the open source ADNI data, where we examine how those who change from MCI to AD differ from those who remain MCI, using visual analytics and machine learning as our main methods. We consolidate the insights from the two efforts into a summary of useful digital protocols and biomarkers for dementia research.

## L1-04: Suppressing both amyloid- $\beta$ and tau is essential to restore neuronal circuit function in an Alzheimer's disease model

**Robert Ellingford**<sup>1</sup>, Samuel S Harris<sup>1</sup>, Marten Kehring<sup>1</sup>, Rikesh M Rajani<sup>1</sup>, Francesca Kar Wey Lam<sup>1</sup>, Lindsay Welikovich<sup>2</sup>, Anita Khasnavis<sup>2</sup>, Rhiannon Laban<sup>1</sup>, Amanda Heslegrave<sup>1</sup>, Umran Yaman<sup>1</sup>, Anastasie Mate<sup>2</sup>, Selina Wray<sup>1</sup>, Dervis Salih<sup>1</sup>, Henrik Zetterberg<sup>1</sup>, Bradley T Hyman<sup>2</sup> & Marc Aurel Busche<sup>1</sup>

<sup>1</sup> UK Dementia Research Institute at University College London, London, UK

<sup>2</sup> Massachusetts Alzheimer's Disease Research Center, Charlestown, Massachusetts, USA

The memory deficits and cognitive decline associated with Alzheimer's Disease (AD) are closely correlated with the widespread accumulation of both amyloid-beta ( $A\beta$ ) and tau pathology across cortical-hippocampal circuits. However, whether this dysfunction arises from a synergistic interaction between these two proteins, and whether it is reversible following treatment, remains unknown. We employed two-photon calcium imaging alongside multi-regional Neuropixels electrophysiology to determine the combined impact of concurrent  $A\beta$  and tau pathology upon the function of cortical-hippocampal circuits *in vivo*, showing that concurrent accumulation of both pathologies acts to promote a strong circuit-wide hypoactivity phenotype across excitatory and fast-spiking inhibitory neurons in multiple mouse models of AD. We also assessed whether these associated deficits can be rescued following suppression of  $A\beta$  and tau expression, demonstrating that reducing individual proteins has no impact on neuronal dysfunction while combined reduction of both pathologies is sufficient to reinstate normal activity patterns. Finally, we employed additional immunohistochemistry, biochemistry and blood plasma analysis to assess the effect of  $A\beta$  and tau suppression on AD biomarkers and investigate the mechanisms underlying the rescue of neuronal activity. We demonstrate that alongside a reduction in soluble AD-associated biomarkers, suppression of  $A\beta$  and tau caused an increase in the density and function of synaptic NMDA receptors. Thus, our data suggest that an NMDA receptor-mediated synaptic mechanism underpins the synergy between  $A\beta$  and tau in AD and provide supportive experimental evidence that therapeutic strategies suppressing both pathologies simultaneously, rather than individual proteins alone, may better restore neuronal circuit function and provide greater clinical benefits to cognitive function in patients.

## L1-05: Characterization of brain barrier fluorescent reporter mouse models of cerebral amyloid angiopathy

Linh Tran, Urban Deutsch, Britta Engelhardt, Steven T. Proulx

Theodor Kocher Institute, University of Bern, Switzerland

There has been a renewed focus on the role of central nervous system (CNS) fluids and barriers in neurological disorders such as cerebral amyloid angiopathy (CAA). A body of suggestive evidence has indicated a link between impaired amyloid- $\beta$  ( $A\beta$ ) clearance and CAA formation, highlighting a fundamental need to improve our insights into the mechanisms of brain clearance. Nonetheless, the mechanisms for fluid circulation and solute exchange in the brain parenchyma remain highly debated and poorly understood. In many studies, full consideration of the brain barriers that compartmentalize the CNS is lacking. With this project, we aim to provide new transgenic mouse models marking the brain barriers that will help us to fill these critical knowledge gaps between CNS fluid clearance and CAA progression. Two novel specific dual-reporter mouse strains: one visualizing CNS vasculature using Claudin5-GFP (cerebral blood vessels) and Prox1-TdTom (lymphatic vessels) and one marking the brain borders with Aqp4-mRuby3 (for astrocyte endfeet of the glia limitans) and VE-cadherin-GFP (for the leptomeninges and blood vessels), were successfully crossed with an ArcA $\beta$  transgenic mouse line, which has resulted in two novel triple-transgenic models of cerebral amyloidosis. In the first stage, A $\beta$  deposition was observed in correlation with changes of brain barrier marker fluorescent expression using ex vivo imaging on decalcified skull or fixed brain sections at different ages (early vs chronic stage of disease). Secondly, solute drainage pathways from the interstitial fluid space were investigated through evaluation of tracer distribution at various timepoints after infusion into different brain regions and the CSF space. Our preliminary results demonstrate that our novel brain barrier reporter mice enable new perspectives on the understanding of brain clearance in rodent CAA models. Going forward, our histological findings will be validated with multiple in vivo imaging modalities, including two-photon microscopy and synchrotron-based X-ray imaging.

## L1-06: Closed-loop auditory stimulation of deep sleep rescues neuropathological and phenotypic hallmarks in Alzheimer's disease mice

I. Dias<sup>1</sup>, I. Barbaric<sup>1</sup>, M. Siegel<sup>1</sup>, V. Gysin<sup>1</sup>, T. Rêgo<sup>1,2,3</sup>, C. R. Baumann<sup>1,3,4</sup>, C. Sanicani<sup>1</sup>, H. Enkerli<sup>1</sup>, D. Noain<sup>1,3,4</sup>

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<sup>3</sup> Neuroscience Center Zurich (ZNZ), Switzerland;

<sup>4</sup> Center of Competence Sleep and Health (SHZ), University of Zurich (UZH), Switzerland.

Sleep alterations are hallmarks of prodromal Alzheimer's disease (AD), with fundamental pathological processes such as protein accumulation and cognitive decline displaying susceptibility to deep sleep modulation. However, the clinical upscaling of pharmacotherapy-based deep sleep enhancement has been hindered by specificity and misuse issues, thus advocating for nonobtrusive slow-wave activity (SWA) boosting methods that would additionally enable preclinically investigating the links between deep sleep and neurodegeneration. In this line, we have recently introduced mouse closed-loop auditory stimulation (mCLAS), successfully increasing SWA during deep sleep and acutely rescuing hallmark sleep-wake disturbances in AD mice. However, would such rescue, if prolonged in time, trigger the prevention or restoration of the cognitive deficits, pathological protein burden and neuronal loss characterizing AD? Here, we explored the effect of 10-day mCLAS (mock: mock-mCLAS, or up-phase: up-mCLAS) on sleep deficiencies, cognitive ability, pathological protein load, and neurodegeneration in AD mice. We found that up-mCLAS consistently rescues sleep impairments in AD mice, prompting increases in NREM sleep time and long/short bout ratio, while promoting decreased NREM sleep fragmentation and microarousals. Notably, up-mCLAS also appears to prevent cognitive decline in AD mice, who maintain performance in a spatial working memory task at control level, as opposed to mock-mCLAS-treated AD mice whose performance declines over time. Additionally, toxic A $\beta$  deposition in the brain and retina of up-mCLAS-treated AD mice is reduced, along with preliminary evidence of prevented locus coeruleus (LC) volume loss, consistent with prevented neurodegeneration. Overall, our results suggest that prolonged up-mCLAS prompted a sleep-mediated neuroprotective effect in AD mice, halting disease progression during an ideal prodromal window susceptible to SWA modulation. To the best of our knowledge, this is the first account of neurodegeneration arrest/prevention via noninvasive sleep modulation, suggesting CLAS may become a future cornerstone of boosted SWA-based therapies for neurodegenerative diseases.

## L1-07: Blarcamesine: A new oral treatment approach for Alzheimer's disease

**Audrey Gabelle**<sup>1</sup>, Stephen Macfarlane<sup>2</sup>, Timo Grimmer<sup>3</sup>, Luca Villa<sup>4</sup>, Elizabeth Gordon<sup>4</sup>, Thomas Jubault<sup>4</sup>, Nicolas Guizard<sup>4</sup>, Kun Jin<sup>5</sup>, William R. Chezem<sup>5</sup>, Christopher U. Missling<sup>5</sup>, Marwan N. Sabbagh<sup>6</sup>

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The ANAVEX2-73-AD-004 phase IIb/III trial was a randomized, double-blind, placebo-controlled study lasting 48 weeks. It evaluated the efficacy and safety of blarcamesine, an oral sigma-1 receptor agonist aimed at restoring autophagy, in patients with early-stage Alzheimer's disease (AD). A total of 508 patients were randomized to receive either blarcamesine (30 mg or 50 mg; n = 338) or placebo (n = 170) once daily by mouth. The primary endpoints were changes in ADAS-Cog13 and ADCS-ADL scores. Secondary endpoints included CDR-SB score and biomarkers such as the plasma A $\beta$ 42/40 ratio and brain volume measured by MRI. Analyses were conducted using mixed models for repeated measures, Welch's t-test, and general linear models. Among the 462 participants in the intent-to-treat (ITT) population (average age: 73.7 years; 48.7% women), 73.1% completed the trial. The blarcamesine group showed statistically significant improvements on the ADAS-Cog13 (-2.027; P = 0.008) and CDR-SB (-0.483; P = 0.010). The ADCS-ADL showed a positive trend, though it was not statistically significant. Treatment positively impacted the plasma A $\beta$ 42/40 ratio and reduced brain atrophy. A genetic analysis revealed an even greater benefit (49.8%) in patients with the wild-type SIGMAR1 gene. The safety profile was favorable. Blarcamesine may represent a promising new oral therapeutic option for early-stage AD, either as a complement to or an alternative to current anti-amyloid treatments.

## L1-08: Designing integrated care pathways in Ticino and Moesano: Mapping entry points and nodes through a participatory approach

**Amati Rebecca**<sup>1</sup>, Pedrini Maribel<sup>1</sup>, Spagnoli Viviana<sup>2</sup>, De Benedetti Anna<sup>3</sup>, Saredo-Parodi Antonio<sup>4</sup>, Cramer Stevens<sup>2</sup>, Fiordelli Maddalena<sup>1</sup>

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**Background:** The growing number of individuals with dementia in Switzerland represents a pressing public health challenge. The CoPeC (Building Care Pathways for Dementia: An Integrated and Participatory Approach to Preserving Autonomy) project, funded by Health Promotion Switzerland, aims to formalize and communicate integrated care pathways in Ticino and Moesano that foster early recognition, slow cognitive decline, and preserve autonomy. We present findings from the project's first work package: Mapping entry points into the care pathway and identifying key interconnections and critical nodes.

**Methods:** CoPeC adopts a phenomenological, participatory, and bottom-up approach, grounded in a quadruple perspective. This includes the professional viewpoint, explored through interactive workshops focused on existing practices and challenges; the caregiver experience, captured via an online survey and focus groups with formal and informal caregivers; expert insight, developed through a Delphi study to build consensus on care priorities; and the institutional perspective, derived from an analysis of relevant official documents. Together, these perspectives ensure that pathway development is anchored in lived experience and contextual knowledge.

**Results:** This presentation focuses on the professional perspective. During two workshops held at Forum Alzheimer 2025 in Lugano, approximately 120 participants discussed in groups and used an interactive digital tool to map resources and areas for improvement across five phases of the dementia journey. The phases "supporting" and "living" appeared well-resourced, while "preventing," "diagnosing," and "dying" appeared less well-resourced. Recurring issues included poor service coordination, limited communication, insufficient funding, and low public awareness.

**Discussion:** These findings, integrated with insights from the other three perspectives, contribute to a comprehensive understanding of the dementia care continuum. CoPeC's participatory framework enables the co-design of context-sensitive care pathways that build on existing services while centering the voices of those most affected. Ultimately, this approach aims to inform a more coordinated, responsive, and person-centered system of dementia care.

Friday, 7 November 2025 | 03:15 – 04:00 PM

## L2-01: Elucidation of amyloid-beta's gambit in oligomerization

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**Aim:** The modest therapeutic efficacy reported with some anti-amyloid-beta (A $\beta$ ) antibodies emphasizes the strong need for an improvement of next generation disease modifying-therapies for Alzheimer's disease (AD).

**Findings:** Using advanced technologies in high resolution mass spectrometry (MS) we were able to shed light on an enigma associated with SDS-PAGE stable A $\beta$  oligomers. Here we provide strong analytical proof of novel A $\beta$  target hotspots present in neurotoxic A $\beta$  oligomers. We show that the early appearance of specific A $\beta$  species, rapidly seed the formation of oligomers, which eventually leads to the formation of stable complexes of larger A $\beta$  entities. We applied quantitative MS approaches to elucidate the composition of these A $\beta$  structures and provide for the first-time quantitative data on the composition of A $\beta$  oligomers, which can now be translated and applied for the analysis of human post-mortem brain tissue or CSF samples from AD patients. Comparative antibody binding studies with aducanumab strongly suggest, that there exist A $\beta$  target "loopholes" which can be exploited for the development of new therapeutic antibodies with binding properties against novel target hotspots present in these oligomers. These findings support a novel, unparalleled approach for targeting early, pathological A $\beta$  species prior to the appearance of large, neurotoxic assemblies. We provide here a first example of a new class of monoclonal antibody (clone: JD1), with a unique binding profile that clearly differentiates to the binding properties of aducanumab or lecanemab.

**Conclusion:** Our findings highlight the strong need for identifying additional, molecular mechanisms associated with the early events of A $\beta$  peptide aggregation. This in turn will allow the improvement of antibody-specific target engagement of early, neurotoxic A $\beta$  oligomers present in the AD brain or periphery and therefore attenuate or even prevent the pathological progression to severe dementia.

## L2-02: Therapeutic potential of mitochondrial transplantation in a cellular model of tauopathy

**Aline Broeglin**, Anne Eckert, Amandine Grimm

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Neurobiology Laboratory for Brain Aging and Mental Health, Psychiatric University Clinics, Basel, Switzerland

Tauopathies are neurodegenerative diseases characterized by an abnormal accumulation of the protein tau in cells, leading to significant neuronal death and cognitive impairment. An important feature of these tau-related diseases is the deficits in bioenergetic functions due to the impairment of mitochondrial integrity. Mitochondria are involved in many cellular processes, including adenosine triphosphate (ATP) synthesis. They are critical in the brain, which consumes much of the body's energy. It has been shown that mitochondrial dysfunctions precede cognitive deficits in these diseases. Therefore, mitochondria are considered a therapeutic target to prevent the development of brain disorders.

A new therapeutic approach is to consider mitochondria as the treatment itself with mitochondrial transplantation. This involves isolating healthy mitochondria and transplanting them into damaged organs or cells using various methods. Our project aims to investigate the therapeutic potential of mitochondrial transplantation in a cellular model of tauopathies.

We used the neuroblastoma cell line SH-SY5Y as recipient cells for the transplantation and the astrocytic cell line A172 as a donor of healthy mitochondria. Cellular and molecular biology tools, as well as fluorescence microscopy experiments, were used during the investigations.

We show that the functional integrity of isolated mitochondria is maintained after the isolation process, and that isolated mitochondria can enter the recipient cells. An optimal treatment concentration was determined, and an increase in cellular viability and bioenergetic functions of the healthy and tauopathy cellular model was observed. Moreover, an improvement in the neurite outgrowth has been detected in both cellular models.

Mitochondrial transplantation offers a new therapeutic approach in tauopathies by considering mitochondria as the treatment itself. Further investigations are needed to explore the cellular mechanisms underlying this phenomenon.

## L2-03: Biological characterization of Frontotemporal Dementia (FTD) using human induced Pluripotent Stem Cells (hiPSCs): an innovative approach of the Swiss FTD network

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Human induced pluripotent stem cells (hiPSCs) hold a great potential for treating neurodegenerative diseases, such as frontotemporal dementia (FTD) – the second cause of neurodegenerative dementia in individuals younger than 60 - due to their ability to differentiate into various cell types found in the central nervous system. By generating patient-specific hiPSCs and directing their differentiation into neuronal populations, personalized disease models can be created, offering unique opportunities for drug screening, disease mechanism understanding, and potential cell-based therapies.

After an initial single case study where we thoughtfully described a novel missense progranulin (*GRN*) mutation in a behavioral variant FTD (bvFTD) with biological hallmarks of TDP43-FTD with an hiPSC model, we introduced this technique with various selected FTD patients in Lausanne, with phenotypes ranging from progressive supranuclear palsy (PSP) to semantic dementia (SD).

Having established this technique by bringing together the clinical data of the Leenaards Memory Center in Lausanne University Hospital and the innovative development of the iPSC platform in the Center for Psychiatric Neuroscience (CPN) in Lausanne University Hospital, we aim at implementing it at a national level bringing together the clinical expertise of members of the Swiss-FTD network to our local knowledge.

## L2-04: Uncoupling between tau deposition and hypometabolism in the brain explains heterogeneity in Alzheimer's disease

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Although neurodegeneration is mostly driven by tau pathology in Alzheimer's disease (AD), other factors modulate neurodegeneration contributing to the variability between tau and neurodegeneration patterns. We investigated the spatial mismatch between tau pathology and hypometabolism as a measure of neurodegeneration and evaluated its impact on phenotypes in 137 amyloid-positive and clinically impaired patients from Geneva Memory Clinic (N=57) and ADNI (N=80), who underwent both 18F-Fluorodeoxyglucose(FDG)-PET and 18F-Flortaucipir-PET within one year. Patients were classified having matched or mismatched pathology based on Dice coefficient between voxel-wise comparisons versus control groups. In case of mismatch, the more extended map defined the prevalent pathology. Differences in demographic and clinical features, neuroimaging-derived features, fluid biomarkers and cognitive trajectories were tested between groups.

We identified 22 patients with spatial match and 115 with mismatch, of which 23 were hypometabolism-predominant and 92 tau-predominant. Match cases were younger, more cognitively impaired and with a steeper cognitive decline, higher amyloid, neocortical tau, cortical atrophy, and level of glial fibrillary acidic protein (GFAP) in plasma, compared to both mismatch groups. Focusing on differences between the hypometabolism- and tau-predominant mismatch cases, the former showed less amyloid and tau burden, but a trend for higher GFAP than tau-predominant cases. We did not find differences in white matter lesion volumes and alpha-synuclein in cerebrospinal fluid, but hypometabolism-predominant cases showed neurodegeneration out of proportion to tau, as measured by differences in z-scores, in medial temporal lobe (MTL), as supportive biomarker for limbic-predominant age-related TDP-43 encephalopathy (LATE).

Spatial matching between hypometabolism and tau deposition was associated with a more severe clinical and biomarker phenotype and a worst prognosis. Hypometabolism-predominant patients had lower AD pathology and disproportionate MTL neurodegeneration to tau suggesting other contributors to neurodegeneration, namely LATE. Spatial match between tau deposition and hypometabolism can identify different phenotypes and inform about possible copathologies in AD.

## L2-05: Slow wave–spindle coupling during deep sleep is uniquely linked to plasma amyloid- $\beta$ levels in older adults

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Slow wave activity, the signature of deep sleep, has consistently been linked to amyloid-beta ( $A\beta$ ), a pathophysiological marker of neurodegeneration. Less is known about how  $A\beta$  relates to specific microstructural processes within deep sleep, such as the coupling of slow waves and spindles, where better functioning reflects younger age, increased memory, and less brain atrophy.

47 older adults (agemean = 70.5 (0.68)) ranging in cognitive functioning completed one adaptation and one baseline night. A subsample (n=39, agemean = 70.5 (0.74)) additionally underwent a three-night acoustic stimulation intervention to boost slow wave activity. Blood samples post-baseline and post-intervention were analyzed for  $A\beta$  1-42/1-40-ratio.

Irrespective of cognitive functioning levels, slow wave–spindle coupling was the best predictor for baseline  $A\beta$ , better than slow wave activity, age or cognitive functioning. Specifically, better  $A\beta$ -levels were linked to a coupling physiology resembling a younger brain. While intervention-induced increases in slow wave activity were linked to a beneficial  $A\beta$ -response across all cognitive levels, increases in slow wave–spindle coupling benefited  $A\beta$ -response exclusively in cognitively impaired individuals.

Our results suggest a link between SW–spindle coupling and  $A\beta$  that goes beyond slow wave activity. This hints towards a potential specific function of SW–spindle coupling related to the early pathophysiology of neurodegeneration.

## L2-06: Memories fade, traces remain: Neural and behavioural correlates of forgotten episodic memories found after 6 months with 7T fMRI

Konstantinos Ioannis Zervas, Tom Willems, Shawn Hiew, Katharina Henke

University of Bern, Bern, Switzerland

Episodic memories fade rapidly after learning, with the majority forgotten within 24 hours, yet we hypothesized that memory traces (engrams) of the forgotten information persist within the human brain's episodic memory system. We investigated the long-term fate of 96 newly learned face-object associations over a six-month period in 40 young, healthy participants. Using 7T whole-brain fMRI, we tracked memory traces as they are formed and retrieved 30 minutes, 24 hours, one week, and six months later. During each retrieval trial, participants rated their memory confidence. Responses rated as 'guessed' were classified as forgotten. At 30 minutes post-encoding, 33% of associations were forgotten; this slightly decreased to 31% at 24 hours, before rising to 38% at one week and 46% at six months. Although retrieval accuracy for guessed responses remained at chance across all intervals, underlying memory traces persisted within the episodic memory network, including hippocampal and prefrontal regions. Both their reactivation and hippocampal-prefrontal connectivity significantly correlated with guessing retrieval accuracy. Memory traces of forgotten associations closely matched the location and shape of those supporting consciously accessible memories, but they were thinner and showed greater changes over time. In contrast, traces associated with accessible memories remained more stable and showed strong recruitment of the neocortex as early as 30 minutes following encoding. These findings suggest that ostensibly forgotten memories persist in the brain although they are no longer accessible to conscious awareness. Thus, forgetting may reflect a loss of conscious access rather than a loss of the underlying information itself.

## L2-07: Preliminary data on power spectral analysis of resting-state EEG in cognitive decline and healthy aging

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Mild cognitive impairment (MCI) is the transitory stage between normal aging and dementia, affecting 10-20% of adults aged 65 and older. Despite its prevalence, the mechanisms underlying the MCI stage of cognitive decline remain largely unclear. Resting-state electroencephalography (EEG) power spectral analysis is a widely used technique to investigate functional brain changes associated with cognitive decline and aging. Previous research indicates that Alzheimer's Disease (AD) is characterized by increased power in slow-wave (delta and theta) and decreased power in fast-wave (alpha and beta) frequencies. Similar, though less consistent, spectral patterns have been observed in individuals with MCI. In contrast, healthy aging is generally associated with reduced slow-wave and alpha activity, alongside increased beta power. In this preliminary study, we performed a power spectrum analysis of resting-state EEG recordings from three groups: individuals with MCI, healthy older adults, and healthy younger adults. High-density EEG recordings (257 channels) were obtained from 30 participants in total (N=10 per group) during a 5-minute resting-state with eyes closed and analyzed using the Welch method across frequencies between 1 to 70 Hz. Preliminary uncorrected results revealed a reduction in alpha power in both MCI and healthy older adults over occipital and temporal regions, consistent with typical age-related neural changes. MCI patients also showed increased theta power compared to healthy controls over frontal and right temporal regions, indicating EEG slowing. Interestingly, beta power increased in MCI patients compared to healthy controls over frontal, parietal, and occipital regions, in contrast to previously reported reductions in AD. These findings suggest that early cognitive decline in MCI may primarily involve increases in slow-wave activity, while decreases in fast-wave activity may occur later during progression toward AD.

# Swiss Network for Dementia Research

## About us

The Swiss Network for Dementia Research is an association established in October 2023 by Dementia Research Switzerland – Synapsis Foundation. The network is grounded in the belief that pooling resources and promoting interdisciplinary knowledge exchange will drive innovation in dementia research and care. Our mission is to foster a collaborative culture, enabling the discovery of new insights and accelerating their application in clinical practice.

We aim to connect dementia experts across disciplines and institutions throughout Switzerland, creating a national network that bridges gaps in dementia research and care. To facilitate collaboration, we offer services such as a community platform, networking events, and communication channels. Our bottom-up approach ensures that our services are tailored to the needs of the community.

Discover our platform and events and support our mission by becoming a member.

## Community platform

The goal of our community platform is to serve as a centralized hub for dementia research and care in Switzerland, connecting all key stakeholders and fostering interdisciplinary collaboration. The platform provides an overview of experts in the field, ongoing projects, current initiatives, and available job and funding opportunities, as well as upcoming events. It also serves as a resource hub, pooling resources—such as biosamples, animal models or diagnostic tools—to create synergies that support both research and care efforts.



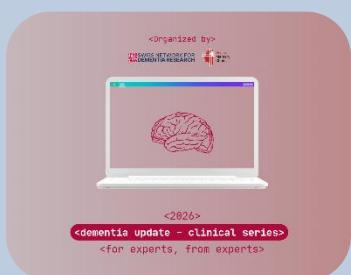
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## Dementia Update Series



The **Dementia Update Series** comprises two virtual formats designed to foster collaboration and knowledge exchange in dementia research and care.

The *Dementia Update – Virtual Series*, launched in February 2025, brings together researchers from basic, clinical, translational, and care sciences, as well as healthcare and industry professionals, to share recent findings, innovations, and services.



The *Dementia Update – Clinical Series*, developed in collaboration with the Swiss Memory Clinics and launching in 2026, is primarily tailored for healthcare professionals and covers clinically relevant topics across disciplines.

Each session in both formats features an expert presentation followed by an interactive discussion to encourage an interdisciplinary dialogue.

# Posters

## Poster Key

A: Diagnosis & Biomarker  
B: Pathophysiological Mechanism  
C: Genetics  
D: Therapy & Intervention  
E: Care  
F: Prevention  
G: Behavior and Cognition

### Presentation time:

- Even number: 17:30 – 18:45
- Odd number: 18:45 – 20:00
- Please install your poster on 6 November 2025 before 3pm.

## Overview

- P1-A Affinity-Based Isolation and One-Pot Analysis of Extracellular Vesicles from Biofluids Using Phase Separated Zwitterionic Coacervates
- P2-A Biobank Operations at Geneva University Hospital's Memory Center
- P3-A Cerebrospinal fluid macrophages can serve as a surrogate to brain parenchymal microglia in vivo
- P4-A Chemical profiling of amyloid beta aggregates in body fluid of Alzheimer's Dementia patients
- P5-A Cognitive Decline linked to region-specific Fronto-Temporal Atrophy in Mild Cognitive Impairment: Insights from Voxel-Based Morphometry
- P6-A Cognitive Impairment in Diabetes: Contributions of Alzheimer's Disease and Cerebrovascular Factors
- P7-A Deciphering fluorescence microscopy datasets with AI
- P8-A Detecting cognitive changes through continuous digital monitoring: Role of AI and visual analytics
- P9-A Elucidation of Amyloid-Beta's Gambit in Oligomerization.
- PX-A Emerging Dementia Biofluid Biomarker Candidates Identified in Human Proteomic Studies (2021-2025) → Poster at the Olink booth
- P10-A Enhanced ALS and FTD Diagnosis Through Integration of the pTau:tTau Ratio with Clinical Biomarkers
- P11-A Evidence for sleep-mediated homeostasis failure in levodopa-induced dyskinesia
- P12-A EVINDER Project: Leveraging the CLEMENS Registry to Link Plasma Biomarkers, BNA Classification, and Clinical Profiles at the Centre Leenaards Memory Center
- P13-A Exploring noradrenergic signaling and sleep patterns in prodromal stages of Alzheimer's disease mouse models
- P14-A Fingerprinting Tau Oligomers with a 20 nm Diameter Nanopore from Pneumolysin
- P15-A Identification of Vascular Dementia-specific protein biomarkers using nanoanalytics
- P16-A Idiopathic Normal Pressure Hydrocephalus: The Interest of Sulcal-Based Morphometry
- P17-A Intravascular Lymphoma Mimicking Inflammatory Cerebral Amyloid Angiopathy
- P18-A Modeling Familial and Sporadic Alzheimer's Disease Using Human iPSC-Derived Neurospheres to Reveal Disease-Specific  $\beta$ -Amyloid Pathology and Gene Expression Signatures
- P19-A Modelling (i.e. IHME) or measuring (i.e. SwissDEM) dementia occurrence?
- P20-A Multicenter Evaluation of the NeuroLF Brain PET System: Initial Real-World and Clinical Trial Data
- P21-A Plasma Biomarkers and Comorbidity-Driven Cognitive Decline: Insights from the A4B Community-Based Dementia Cohort in Sub-Saharan Africa

- P22-A** Quantitative assessment of I-123-ioflupane uptake using absolute and relative SUV in the diagnosis of dementia with Lewy bodies
- P23-A** Reduced levels of the sigma-1 receptor in the brains of Alzheimer's disease patients: associations with synaptic loss, amyloid-beta and tau
- P24-A** ROMENS: An Automated Regional Real-World Data Registry for Dementia Research and Clinical Care in Western Switzerland
- P25-A** Screening of Alzheimer's Disease Using an AI-Driven Platform: Study Design and Preliminary Results from the Geneva Site of the PREDICTOM Study
- P26-A** The OMICS-AD multimodal biomarker cohort study: design, methods, and cohort characteristics
- P27-A** The quest for the best: manual, atlas- and spatial prior-based detection of locus coeruleus
- P28-A** Uncover Lewy Body Disease with Neurotechnology
- P29-B** Altered Excitation/Inhibition in the Prefrontal Cortex of Alzheimer's Disease Mouse Model During REM sleep
- P30-B** Astrocytic SHANK3 loss as an early driver of striatal circuit failure in Huntington's disease
- P31-B** Brain apoE particle composition defines its functions
- P32-B** Cerebral Small Vessel Disease in Early vs Late Onset Alzheimer's Disease
- P33-B** Characterization of brain barrier fluorescent reporter mouse models of cerebral amyloid angiopathy
- P34-B** Dissecting the role of microglial TDP-43 in demyelination and lipid handling
- P35-B** Electrophysiological markers of network communication in an Alzheimer's disease mouse model with early tau pathology
- P36-B** From Liver to Brain: How Hepatic Dysfunction Fuels Neurodegeneration
- P37-B** Generation of Seed-Independent, Reversible  $\beta$ -Sheeted Tau Aggregation in an Inducible H4 Cell Line
- P38-B** Light mediated CDK5 repression and its potential effects on the circadian clock and Alzheimer's disease.
- P39-B** Linking Brain Networks to Tau Propagation in Alzheimer's Disease
- P40-B** Longitudinal cardiovascular risks and their impact on white matter hyperintensities
- P41-B** Mitochondrial Transfer between Astrocytic and Neuronal Cells Is Impacted By Abnormal Tau Protein
- P42-B** Molecular, genetic and functional screening to identify modifiers of neurodegenerative diseases
- P43-B** Perivascular spaces in memory center patients with dementia with Lewy bodies and Alzheimer's disease
- P44-B** Protein fingerprints of brain-derived extracellular vesicles predict types of tau pathology
- P45-B** Restoring the Neurogenic Niche: Astrocytic Modulation of Microglial Reactivity in Alzheimer's Disease
- P46-B** Sortilin 1 modulates ApoE levels and tau seeding in an astrocytic model
- P47-B** Stopping Parkinson's disease at early stages
- P48-B** Structure-function relationship of alpha-synuclein fibrils derived from distinct synucleinopathies
- P49-B** Testing the Amyloid Cascade in Alzheimer's Disease: Insights from AA-2024 Biological-Clinical Criteria
- P50-B** Tract-Specific Microstructural Vulnerability Linked to Vascular Risk and White Matter Hyperintensities
- P51-B** Two-photon calcium imaging reveals increased local propagating calcium waves in cerebral organoids with APP mutation
- P52-C** Biological characterization of Frontotemporal Dementia (FTD) using human induced Pluripotent Stem Cells (hiPSCs): an innovative approach of the Swiss FTD network
- P53-C** Cognitive rejuvenation through partial reprogramming of engram cells
- P54-C** Investigation of genome engineered humanized ALS/FTD Drosophila models
- P55-C** Pathogenicity of a missense GRN variant in Frontotemporal Dementia

- P56-D** Anti-amyloid drugs for patients with idiopathic Normal Pressure Hydrocephalus and positive Alzheimer's disease biomarkers?
- P57-D** Blarcamesine: A New Oral Treatment Approach for Alzheimer's Disease
- P58-D** Brain mechanisms underlying closed-loop auditory stimulation during slow-wave sleep in a neurodegeneration model
- P59-D** Computational engineering of Bax-inhibiting peptides
- P60-D** Exploring closed-loop auditory stimulation's role in retinal glymphatic clearance in Alzheimer's Disease model mice
- P61-D** Mechanistic insights of coordination cage-mediated siRNA-delivery in Alzheimer's disease. A multidisciplinary approach from synthesis and simulations to in vivo validation
- P62-D** Metformin and Its Analogues in Autophagic Degradation of  $\alpha$ -Synuclein Condensates
- P63-D** Microbial Modulation of the Gut-Brain Axis in Alzheimer's Disease
- P64-D** Overexpression of UCP4 in astrocytes induces fatty acid oxidation for mitochondria respiration fuelling
- P65-D** Recruitment, enrollment and retention strategies in Clinicals Trials: The Geneva Memory Center experience
- P66-D** Remote technologies in early stages of Alzheimer's disease: feasibility, usability and acceptance of an app-based cognitive training
- P67-D** Restoring mitochondrial homeostasis as a therapy for Alzheimer's disease
- P68-D** Targeting Neuroinflammation and Tau/APP Pathology via Intranasal Delivery of Azilsartan Medoxomil Nanoemulgel in A $\beta$ 1-3-induced Alzheimer's Dementia Model
- P69-D** Targeting slow-wave sleep dynamics: closed-loop auditory stimulation as a translational tool for neurodegeneration
- P70-D** Therapeutic potential of mitochondrial transplantation in a cellular model of tauopathy.
- P71-D** Treatment-resistant depression in older adults: associated socio-demographic factors, dementia risk and therapeutic approaches
- P72-E** Exploring pain, anxiety and adverse effects associated with lumbar puncture in a memory clinic population: a prospective longitudinal study
- P73-E** MemoApp: AI-Supported Telehealth for Personalized, Home-Based Dementia Care
- P74-E** Palliative and end-of-life care for dementia patients in a Swiss psychiatric hospital.
- P75-E** Telemedicine for Older Adults: A Pilot Study on the Usability and Acceptability in Remote Cognitive Assessment
- P76-E** The language of care: what metaphors reveal about the experiences of dementia (in)formal caregivers
- P77-E** Toward Measurable Dementia Competence: A Delphi Study to Develop Indicators for Quality Dementia Care
- P78-E** Unlocking the Potential of Electronic Health Records for Dementia Research: Insights from the Clinical Record Interactive Search (CRIS) Platform
- P79-F** An integrated action plan for dementia prevention in Geneva: the cognitive pillar of the Swiss Brain Health plan
- P80-F** Enhancing Cognitive and Physiological Health in Older Adults Through Social Interaction
- P81-F** Enhancing Motivation for Dementia Prevention: A Digital, Value-Based Just-in-Time Adaptive Intervention Framework
- P82-F** Implementing a Primary Dementia Prevention Program in Geneva: Feasibility and Preliminary Outcomes
- P83-F** Preventing cognitive decline using portable, non-invasive sleep enhancement.
- P84-F** Slow wave-spindle coupling during deep sleep is uniquely linked to Plasma Amyloid- $\beta$  levels in Older Adults
- P85-F** The Brain Health Registry: A Resource for Swiss Research on Alzheimer's and Dementia
- P86-F** The evolving potential for dementia prevention in Switzerland: population attributable fractions of risk factors over time
- P87-G** 24-hour movement behavior of institutionalized people with moderate to major neurocognitive disorders
- P88-G** Beyond "Dementia": Reimagining Nomenclature for Cognitive Health

- P89-G** Gender matters in the Association Between Subjective Cognitive Complaints and Memory in Healthy Ageing
- P90-G** Memories Fade, Traces Remain: Neural and Behavioural Correlates of Forgotten Episodic Memories Found After 6 Months with 7T fMRI
- P91-G** Metacognitive impairment in Subjective Cognitive Decline: Evidence from a Memory Clinic Population
- P92-G** Neural Traces of Forgotten Memories Persist in Humans and are Behaviorally Relevant
- P93-G** Preliminary data on power spectral analysis of resting-state EEG in cognitive decline and healthy aging

## Poster abstracts

Category: Diagnosis and Biomarker

### **P1-A: Affinity-Based Isolation and One-Pot Analysis of Extracellular Vesicles from Biofluids Using Phase Separated Zwitterionic Coacervates**

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Extracellular vesicles (EVs), including brain-derived EVs, hold significant promise for liquid biopsy applications, particularly in the diagnosis and monitoring of neurodegenerative diseases such as Alzheimer's, Parkinson's, and Amyotrophic Lateral Sclerosis. However, their heterogeneous nature presents a major bottleneck to clinical translation, complicating their efficient and selective isolation from complex biofluids.<sup>1</sup>

Here, we introduce a robust EV isolation method based on phase-separated zwitterionic (ZW) coacervates. These coacervates form across a broad range of pH and ionic conditions, ensuring compatibility with diverse biological fluids.<sup>2</sup> Their intrinsic antifouling properties reduce nonspecific binding, enabling the selective capture of EVs when functionalized with affinity probes. We demonstrate this approach using a membrane-sensing peptide—a pan-specific probe targeting the high-curvature lipid bilayer of EVs—to overcome the variability in EV surface marker expression.<sup>3</sup> This strategy is applied to pull down and release EVs from untreated serum, cerebrospinal fluid, and urine, achieving high yields and preserving vesicle integrity.

We demonstrate the method's utility both as a preparative step for downstream analysis and as a one-pot assay using flow cytometry, significantly streamlining pre-analytical workflows.<sup>2</sup> Both approaches are employed to profile EV-associated biomarkers and to distinguish clinical cohorts of neurodegenerative disease patients. Overall, functionalized ZW coacervates offer a powerful platform for selective EV isolation and direct analysis from complex samples, advancing the development of EV-based diagnostics.

## **P2-A: Biobank Operations at Geneva University Hospital's Memory Center**

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The Biobank at Geneva University Hospital's Memory Center is a key infrastructure supporting translational research in neurodegenerative diseases, particularly Alzheimer's disease and related disorders. To date, the biobank has collected over 10,000 cerebrospinal fluid (CSF) samples, 40,000 blood-derived samples (including plasma, serum, and PAXgene), 18,000 stool samples, and 4,000 DNA samples extracted from both blood and stool. These biospecimens are linked to comprehensive clinical datasets from more than 2,000 participants.

Participants are categorized into diagnostic groups including Mild Cognitive Impairment (MCI), dementia, and cognitively healthy controls, with detailed medical histories, neuropsychological assessments, and imaging data systematically recorded. This rich dataset enables longitudinal studies on disease progression, biomarker discovery, and personalized medicine approaches.

The biobank operates under a robust ethical and legal framework, ensuring informed consent, data anonymization, and full compliance with Swiss federal regulations and international standards. It is certified under ISO quality management systems and adheres to the best practices promoted by the Swiss Biobanking Platform (SBP), the national infrastructure for biobanking excellence. These certifications guarantee high-quality sample handling, traceability, and interoperability with national and European research networks.

This poster outlines the operational model of the biobank, including patient recruitment, sample logistics, data integration, and governance. The infrastructure is supported by secure IT systems and a multidisciplinary team committed to scientific rigor and ethical integrity. By providing access to high-quality, well-annotated biospecimens, the biobank serves as a cornerstone for cutting-edge research in memory disorders and contributes to the advancement of precision medicine.

### **P3-A: Cerebrospinal fluid macrophages can serve as a surrogate to brain parenchymal microglia in vivo**

Eric Morel<sup>1,2,3</sup>, Quentin Amossé<sup>4</sup>, Aurelien M Badina<sup>4</sup>, Benjamin B Tournier<sup>4</sup>, Yan Tang<sup>3</sup>; Ron Stoop<sup>3</sup>; Gilles Allali<sup>1,2</sup>, Giovanni B Frisoni<sup>5</sup>, Philippe Millet<sup>4</sup>, Aurelien Lathuilière<sup>5,6</sup>, **Stergios Tsartsalis**<sup>3,4</sup>

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#### **Aims**

Brain myeloid cells, especially microglia, are important regulators of brain physiology. Genetic and neuropathological approaches indicate that they contribute to the pathophysiology of Alzheimer's disease (AD). However, we lack tools to study them in vivo. Recently, single cell RNA sequencing (scRNAseq) studies revealed the existence of macrophages in the cerebrospinal fluid (CSF), i.e. accessible through lumbar puncture. These CSF macrophages show transcriptomic similarities to microglia and macrophages of the brain parenchyma. We hypothesize that they can serve as surrogate for the study of parenchymal myeloid cells.

#### **Methods**

We performed scRNAseq in patients' CSF samples and re-analysed in vivo CSF and postmortem human brain scRNAseq datasets. We reasoned that the transcriptomic alterations of CSF macrophages from patients with AD, compared to controls, should reflect the alterations of postmortem parenchymal microglia from the same groups of patients. As CSF macrophages are transcriptomically similar to brain microglia, we tested the specificity of this similarity compared to other myeloid cells in the CSF and blood. We thus compared the enrichment of microglia-specific genes among myeloid cell types using expression-weighted cell type enrichment (EWCE). Finally, we investigated if CSF macrophages shared with microglia the enrichment for genes associated to genome-wide association study (GWAS) loci for AD.

#### **Results**

CSF macrophages are present in CSF samples irrespective of the disease status. In AD patients, CSF macrophages show transcriptomic alterations in pathways compatible with the alterations of parenchymal microglia. CSF macrophages uniquely and significantly express microglia-specific genes compared to the other myeloid cells of the CSF and the blood. Finally, CSF macrophages show a significant and specific enrichment for AD GWAS genes, similar to parenchymal microglia.

#### **Conclusion**

CSF macrophages can serve as in vivo surrogates of microglia. Through longitudinal studies, they can reveal alterations with a potentially causal role and accelerate the development of immune-based therapeutics.

## P4-A: Chemical profiling of amyloid beta aggregates in body fluid of Alzheimer's Dementia patients

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Amyloid  $\beta$  ( $A\beta$ ) peptides play a central role in Alzheimer's disease (AD), with isoforms  $A\beta$ -40 and  $A\beta$ -42 exhibiting distinct aggregation pathways. Clarifying the interactions between the two isoforms and differences in protein aggregate morphology in body fluids is key for monitoring disease progression and identifying potential therapeutic targets. We present a multiscale imaging approach combining atomic force microscopy and super-resolution fluorescence microscopy to resolve and chemically distinguish aggregates formed when  $A\beta$ -40 and  $A\beta$ -42 are co-incubated in both phosphate-buffered saline (PBS) and synthetic human cerebrospinal fluid (CSF). At the single-particle level, we show that  $A\beta$ -40 exhibits an inhibitory effect on  $A\beta$ -42 aggregation, likely through co-localization of  $A\beta$ -40 oligomers along the fibrillar structures of  $A\beta$ -42. These findings are supported by FTIR and ThT kinetic aggregation assays. Importantly, we extended our approach to human patient CSF samples and demonstrated that this method can differentiate between the two amyloid isoforms in CSF of patients at both early and late stages of Alzheimer's disease and observe a correlation between aggregate morphology and patients' clinical evaluation. Finally, we are adapting the developed protocols to screen amyloid and tau isoforms in the plasma of patients at various of decline in memory and cognition.

## **P5-A: Cognitive Decline linked to region-specific Fronto-Temporal Atrophy in Mild Cognitive Impairment: Insights from Voxel-Based Morphometry**

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Mild Cognitive Impairment (MCI) is characterized by cognitive decline, particularly in memory, with relatively preserved daily functioning. A key feature of MCI is an accelerated grey matter (GM) volume loss in the fronto-temporal regions, including the hippocampus. Yet, the link between region-specific brain atrophy and behavioral symptoms remains unclear. As part of the MemStim randomized clinical trial, we examined GM volume differences using voxel-based morphometry on T1-weighted MRI scans from 33 individuals with MCI and 58 gender and age-matched healthy controls (HC). As expected, MCI patients performed worse than controls on the Montreal Cognitive Assessment (MoCA), a standardized diagnostic tool for MCI. Exploratory whole-brain analysis revealed widespread GM frontotemporal atrophy in MCI patients, centered on the left hippocampus-amygdala complex. Significant GM reductions were also found in the anterior cingulate cortex, orbitofrontal gyrus, and inferior temporal gyrus. Several cognitive scores were significantly associated with these brain region clusters. Notably, the left hippocampus cluster strongly correlated with episodic memory scores of the Logical Memory Story B test. The right amygdala cluster moderately correlated with the Rey-Osterrieth Complex Figure test scores and the 3-Objects-3-Places test. These preliminary findings highlight the utility of morphometric approaches in characterizing structural brain changes in MCI patients and suggest the value of further investigations into cortical thickness, pathological protein burden, and alterations in network connectivity.

## P6-A: Cognitive Impairment in Diabetes: Contributions of Alzheimer's Disease and Cerebrovascular Factors

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Type 2 diabetes is a risk factor for cognitive decline and dementia, through structural and vascular brain changes that may act in synergy with Alzheimer's disease (AD). This study aimed to assess the contributions of AD biomarkers and cerebrovascular changes to cognition in diabetic vs non-diabetic individuals.

We included 185 subjects from Geneva Memory Center with available amyloid- and tau-PET, MRI exam with T1 and FLAIR sequences, and Mini-Mental State Examination (MMSE). Amyloid and tau status were defined based on PET visual assessment. Indices of vascular pathology, namely white matter lesion volumes were extracted from MRI images and age-related white matter changes (ARWMC) were scored. Four subgroups were defined based on amyloid positivity/negativity and diabetic/non-diabetic status. To evaluate differences across groups, analyses of variance were performed controlling for age, sex, and diagnostic stage (subjective cognitive decline [SCD], mild cognitive impairment [MCI], and dementia). The moderating effect of diabetes on the relationship between MMSE and biomarkers was tested using linear regression analyses with interaction terms, adjusting for the same covariates.

The prevalence of diabetes was 25% (46 subjects). Diabetic individuals showed higher frequencies of MCI and dementia ( $p=0.04$ ), and tau-PET positivity ( $p=0.03$ ), and presented higher ARWMC scores ( $p=0.005$ ). In amyloid-negative individuals, MMSE was significantly lower in diabetic individuals than in those without diabetes ( $p=0.0001$ ). In amyloid-positive individuals, ARWMC scores were significantly higher in diabetics than non-diabetic subjects ( $p=0.001$ ). No significant interaction effects with diabetes were found in the whole group, suggesting that the association between AD biomarkers or vascular pathology and cognitive performance is not modulated by the presence of diabetes.

Our findings suggest that diabetes is positively associated with cognitive impairment, even in non-AD patients, and higher vascular burden, independently of AD biomarkers. Diabetes may contribute to structural and cognitive impairment even in the absence of synergistic effects with AD.

## P7-A: Deciphering fluorescence microscopy datasets with AI

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Despite decades of intensive research into the pathobiology of amyotrophic lateral sclerosis (ALS), effective treatments remain elusive. The reactive transformation of astrocytes (ACs) has emerged as a critical factor in the initiation and progression of various neurodegenerative diseases, including ALS (Liddelov et al. 2017, Taha et al. 2022). Targeting this transformation represents a promising avenue for developing new therapeutic strategies. However, a major challenge lies in identifying and categorizing reactive AC sub-states, which hinders a deeper understanding of their roles in ALS pathology and the design of treatments tailored to these cellular states (Escartin et al. 2021).

In this work, we analyzed fluorescence microscopy data from human induced pluripotent stem cells (hiPSCs) by means of a contrastive deep learning framework (Chen et al. 2020) adapted specifically for microscopy data. Through this approach, we learnt visual representations of ACs in culture in an automated and unbiased fashion without the need of annotations or prior knowledge about the data. These deep learning representations revealed distinct phenotypes enriched in ALS-related mutations and reactive astrocytes, while also capturing ALS- and reactivity-related information consistent across multiple experimental batches.

The resulting atlas will serve as a foundation for developing an AI-enhanced personalized drug screening platform, aimed at identifying small molecules capable of reversing the reactive transformation of ACs. By integrating advanced computational methods with experimental validation, this study highlights key morphological processes underlying reactive AC sub-states in ALS, paving the way for accelerated therapeutic development for neurodegenerative diseases.

## **P8-A: Detecting cognitive changes through continuous digital monitoring: Role of AI and visual analytics**

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Recent developments in computer- and data science domains, specifically the lean applications that can run on mobile devices such as mobile phones and tablets, new artificial intelligence (machine- and deep learning) paradigms, and a new appreciation of designing systems that enable human-AI collaborations offer exciting possibilities also in the world of dementia prediction, monitoring and possibly interventions.

In this talk, we offer insights from two efforts: One is from cognitive data obtained through a mobile app that re-envision cognitive testing augmented reality (AR) and other gamified features (the Altoida App). Our studies reveal that the app picks up signs of conversion from mild cognitive impairment (MCI) to Alzheimer's Disease (AD), and cognitive improvements observed in cardiac patients after a surgery, both of which demonstrate evidence that continuous monitoring is possible and offers unique insights. The second effort is an exploratory study on the open source ADNI data, where we examine how those who change from MCI to AD differ from those who remain MCI, using visual analytics and machine learning as our main methods. We consolidate the insights from the two efforts into a summary of useful digital protocols and biomarkers for dementia research.

## P9-A: Elucidation of Amyloid-Beta's Gambit in Oligomerization

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### Aim:

The modest therapeutic efficacy reported with some anti-amyloid-beta (A $\beta$ ) antibodies emphasizes the strong need for an improvement of next generation disease modifying-therapies for Alzheimer's disease (AD).

### Findings:

Using advanced technologies in high resolution mass spectrometry (MS) we were able to shed light on an enigma associated with SDS-PAGE stable A $\beta$  oligomers. Here we provide strong analytical proof of novel A $\beta$  target hotspots present in neurotoxic A $\beta$  oligomers. We show that the early appearance of specific A $\beta$  species, rapidly seed the formation of oligomers, which eventually leads to the formation of stable complexes of larger A $\beta$  entities. We applied quantitative MS approaches to elucidate the composition of these A $\beta$  structures and provide for the first-time quantitative data on the composition of A $\beta$  oligomers, which can now be translated and applied for the analysis of human post-mortem brain tissue or CSF samples from AD patients. Comparative antibody binding studies with aducanumab strongly suggest, that there exist A $\beta$  target "loopholes" which can be exploited for the development of new therapeutic antibodies with binding properties against novel target hotspots present in these oligomers. These findings support a novel, unparalleled approach for targeting early, pathological A $\beta$  species prior to the appearance of large, neurotoxic assemblies. We provide here a first example of a new class of monoclonal antibody (clone: JD1), with a unique binding profile that clearly differentiates to the binding properties of aducanumab or lecanemab.

### Conclusion:

Our findings highlight the strong need for identifying additional, molecular mechanisms associated with the early events of A $\beta$  peptide aggregation. This in turn will allow the improvement of antibody-specific target engagement of early, neurotoxic A $\beta$  oligomers present in the AD brain or periphery and therefore attenuate or even prevent the pathological progression to severe dementia.

## PX-A: Emerging Dementia Biofluid Biomarker Candidates Identified in Human Proteomic Studies (2021-2025)

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### Background:

- Alzheimer's disease (AD) and other dementias are among the top causes of death globally.
- As the world population ages, the incidence of age-related neurodegenerative diseases is also increasing.
- Recently approved and new AD-modifying treatments promise more years of independence for patients and families affected by dementias. Such treatments highlight the need for biomarkers along the entire drug development and patient care journey.
- There is an unmet clinical need for biomarkers that enable the early detection of AD and other dementias.
- Recent proteomic analyses of biofluids have identified numerous emerging dementia biomarker candidates.

### Aim:

- Identify trends in emerging dementia biomarkers.
- Understand the significance and pathway context of emerging dementia biomarkers for future validation and potential clinical application for improved outcomes.

→Poster presented at the Olink booth

## P10-A: Enhanced ALS and FTD Diagnosis Through Integration of the pTau:tTau Ratio with Clinical Biomarkers

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**Objective:** Amyotrophic Lateral Sclerosis (ALS) and Frontotemporal Dementia (FTD) lack established biomarkers for early and accurate diagnosis, relying predominantly on extensive clinical assessments. The phosphorylated-tau to total-tau ratio (pTau:tTau) has been proposed to discriminate ALS and/or FTD (ALS|FTD) from their mimics. We aimed to identify an optimal set of cerebrospinal fluid (CSF), serum, and available clinical biomarkers that can accurately differentiate ALS|FTD from related neurodegenerative diseases – specifically 4R-tauopathy, Alzheimer's disease, Lewy body diseases, and normal pressure hydrocephalus – as well as from controls.

**Methods:** This retrospective, cross-sectional study analyzed data from 239 patients with suspected neurodegenerative diseases from the Department of Neurology, University Hospital Zurich, who underwent lumbar puncture between 2016-2025. Diagnoses were established based on international consensus criteria or the absence of clinical suspicion of neurodegenerative disease for controls. Extracted data included demographics, disease duration, cognitive performance, CSF biomarker profiles, and relevant comorbidities including head trauma, metabolic, cerebrovascular, autoimmune, and neoplastic disorders. We used XGBoost feature importance to prioritize predictors.

**Results:** The pTau:tTau ratio was lowest in ALS|FTD (mean=0.109±0.033), followed by 4R-tauopathy (mean=0.129±0.034,  $p<0.05$ ), Alzheimer's disease (mean=0.162±0.021,  $p<0.001$ ), and remaining groups (mean=0.134±0.035,  $p<0.001$ ). In ALS|FTD patients, reduced pTau:tTau ratio correlated with increased CSF-serum albumin ratio and less severe medial temporal lobe atrophy. Compared with using the pTau:tTau ratio alone (AUC=0.75), a multivariate model incorporating the pTau:tTau ratio alongside temporal disease characteristics, immunological and amyloid CSF markers, serum albumin, and radiological white matter lesion burden achieved a considerably more accurate ALS|FTD differentiation (AUC= 0.87).

**Conclusions:** This study contextualises the pTau:tTau ratio with blood-brain barrier dysfunction and mesiotemporal structural integrity in ALS|FTD. Integrating CSF biomarkers with clinical and demographic features significantly enhances diagnostic precision beyond conventional approaches. Yet, clinical-biological heterogeneity of ALS and FTD variants might drive additional variation. Prospective validation in larger cohorts and earlier disease stages will be essential.

## P11-A: Evidence for sleep-mediated homeostasis failure in levodopa-induced dyskinesia

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**Introduction.** Slow-wave activity (SWA) during slow-wave sleep (SWS) facilitates synaptic downscaling, while theta activity during wakefulness reflects synaptic potentiation. Levodopa-induced dyskinesia (LID) in Parkinson's disease (PD) is linked to impaired synaptic homeostasis, but whether this stems from defective downscaling, impairing wake-related synaptic buildup, remains unclear. This study mainly focuses on analyzing theta activity during wakefulness to investigate the build-up process in resting state.

**Methods.** We compared actigraphy and high-density EEG in 12 healthy volunteers and three PD cohorts: de novo (n=12), advanced non-dyskinetic (n=13), and dyskinetic (n=11). Participants underwent one-week actigraphy monitoring (i.e., GeneActiv sensors, with sleep metrics extracted via GGIR algorithms) and morning/evening resting-state EEG. Theta power (4–8 Hz) were analyzed using both linear models (LM) and linear mixed-effects models (LMM), adjusted for confounders (e.g., age, gender, LEDD and disease duration). To validate the spatial distribution of significant effects, we applied non-parametric permutation tests combined with Threshold-Free Cluster Enhancement (TFCE).

**Results.** Dyskinetic patients exhibited reduced actigraphy-estimated sleep efficiency ( $p < 0.001$ ), prolonged sleep latency ( $p < 0.05$ ), and increased wake after sleep onset ( $p = 0.01$ ) versus controls. Theta power was higher in dyskinetic patients across all cortical regions during morning sessions (LM-TFCE-corrected  $p < 0.05$ ), with absent diurnal scaling across prefrontal, temporal, and occipital regions (LMM-TFCE-corrected  $p < 0.05$ ) – contrasting controls and non-dyskinetic groups showing progressive theta accumulation.

**Conclusions.** These findings demonstrate for the first time a bidirectional synaptic homeostasis failure in LID: impaired SWA-mediated downscaling coexists with saturated morning theta activity, indicating defective wake-related synaptic potentiation. Our results highlight sleep modulation as a therapeutic priority. By enhancing slow-wave sleep, can we restore the synaptic downscaling, and potentially break the cycle of theta saturation and dyskinesia initiation and/or progression?

## **P12-A: EVINDER Project: Leveraging the CLEMENS Registry to Link Plasma Biomarkers, BNA Classification, and Clinical Profiles at the Centre Leenaards Memory Center**

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Since 10 years, the Leenaards Memory Center, the University Memory Clinic of the Lausanne University Hospital has developed CLEMENS, a mixed-use registry designed to support both clinical care and research in neurodegenerative cognitive disorders. To date, more than 8,000 patients have been included in this registry.

While the availability of data varies across individuals, a substantial number of cases include neuropsychological assessments, morphometric brain MRI, CSF biomarker data (A $\beta$ , Tau), and a structured diagnostic classification based on the BNA model (stage, syndrome, etiology). Among them, over 4,500 patients have signed the general research consent, making them eligible for inclusion in the EVINDER project, which aims to enhance clinical stratification by integrating plasma biomarkers.

In collaboration with the CHUV Genomic Biobank, more than 900 plasma samples have been identified, collected during medical care, sometimes on the day of diagnosis, sometimes several years earlier. Although not all samples have been extracted or analyzed yet, preliminary plasma assays for P-Tau217, GFAP, and NfL already reveal significant variations across BNA profiles, highlighting their potential as biological stratification tools. To support clinical implementation, an interactive platform is under development.

This tool will allow CLM physicians to retrospectively explore plasma biomarker levels in relation to BNA classifications drawn from the CLEMENS registry. This direct integration of biological and clinical data paves the way toward precision medicine in neurodegenerative cognitive disorders and future plasma biomarkers dosages.

## **P13-A: Exploring noradrenergic signaling and sleep patterns in prodromal stages of Alzheimer's disease mouse models**

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The onset of Alzheimer's disease (AD) and of abnormal sleep patterns are signaled by initially minute but ultimately disastrous physiological brain malfunctions. The Locus Coeruleus (LC) belongs to the brain areas that show such malfunctions in the early stages of AD and generates large noradrenaline (NA) signals that are key for wake cognition but also for the sleep architecture in mice. Therefore, insights on how sleep disturbances relate to LC malfunctions could provide sensitive signatures of the earliest stages of AD.

We explore the real-time functionality of the noradrenergic system in APP/PS1, and APP/MAPT knock-in mice with or without neuromelanin expression, using dual fiber photometry in freely behaving animals that express biosensors for free NA levels in the thalamus or the hippocampus (CA1) and for neuronal Ca<sup>2+</sup> fluctuations in LC neurons. In combination with polysomnography (EEG/EMG), we record local field potential (LFP) activity in the somatosensory cortex (S1) and in CA1 to assess vigilance states in mice aged 2-18 months to cover early and late stages of AD.

We investigate sleep architecture parameters, such as time spent in each vigilance state and bout durations. We track how Ca<sup>2+</sup> activity in the LC and its NA output relate to sleep properties. Preliminary data indicate that depending on the mouse line, REMS bouts tend to shorten with aging, indicators such as LC calcium and EMG activity show unusual activity during some REMS bouts, suggesting that REMS might be dysregulated from the prodromal phase. Ongoing work will associate histological signatures of AD progression with these sleep features.

Decoding the patterns of LC's dysfunction during the prodromal phase of AD and their consequences on sleep could prove essential to early diagnosis of AD and for interventions.

## P14-A: Fingerprinting Tau Oligomers with a 20 nm Diameter Nanopore from Pneumolysin

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Biological nanopores are emerging as powerful sensing tools for single-molecule analysis of nucleic acids, peptides, and proteins. However, the limited size of existing biological nanopores presents a long-standing challenge for transporting large-size, full-length proteins in their natively folded state. Here, we introduce a stable, low-noise, cylindrical transmembrane pore formed by self-assembly of Pneumolysin (PLY) toxin. In situ, assembly of the PLY nanopore occurred in a single step directly on a lipid bilayer upon application of a potential difference of 100 mV. Electrical resistance measurements revealed a diameter of approximately  $20 \pm 2$  (N = 50) nm of membrane-inserted PLY nanopores. This exceptionally large nanopore enabled accurate single-molecule resistive-pulse sensing for the estimation of the volume and shape of folded proteins, ranging in size from FAB ( $\approx 50$  kDa) to tetramers of concanavalin A ( $4 \times 28$  kDa = 112 kDa). We used PLY pores to detect differences in the volume of single proteins within a mixture and estimated the size distribution of tau protein (monomer  $\approx 45$  kDa) and its oligomers from dimers to hexamers in solution. By combining volume analysis with single-particle shape approximation, we uncovered details of Tau oligomerization at nanomolar concentrations. The novel PLY nanopore shows strong promise for advancing the quantification and characterization of heterogeneous amyloid oligomers as biomarkers.

## **P15-A: Identification of Vascular Dementia-specific protein biomarkers using nanoanalytics**

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Vascular dementia (VaD) is the second most common type of dementia after Alzheimer's Disease, representing a significant burden on the health and well-being of older people. Although a substantial number of risk factors for VaD have been identified, the pathological mechanisms and protein biomarkers related to the disease remain to be fully clarified. In particular, the discovery and validation of biomarkers in body fluids, including cerebrospinal fluid (CSF), has been challenging, owing to the non-specificity of mechanisms, such as endothelial activation and hypercoagulability, to cerebrovascular injury. In our laboratory, we aim to identify and validate protein biomarkers related to VaD in a diverse cohort of patients at various stages of decline in memory and cognition using nanoscale imaging and chemical spectroscopic techniques, which include Atomic Force Microscopy (AFM), Immunofluorescence Microscopy (IFM), and Fourier Transform Infrared Spectroscopy (FTIR) operating at room temperature. By resolving and quantifying amyloid and tau protein aggregates in CSF as potential biomarkers, we elucidate the pathogenic protein structures and components that differentiate VaD from other neuropathologies, like AD, and correlate protein aggregation with disease progression.

## **P16-A: Idiopathic normal pressure hydrocephalus: The interest of sulcal-based morphometry**

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Introduction: Idiopathic normal pressure hydrocephalus (iNPH) is the leading cause of reversible dementia in the elderly, is characterized mainly by gait disturbances along with ventricular enlargement, and can be treated with shunting procedure. Neuroradiological features rely on visual assessment, including sulcal characteristics. This study applies automatic sulcal-based morphometry to characterize the iNPH sulcal phenotype and to distinguish iNPH patients who respond or not to the cerebrospinal fluid tap test (CSF-TT), a prognostic test to predict response to shunting.

Methods: The study included 32 patients (mean age: 78.9y / Females: 14) diagnosed with iNPH and 41 healthy controls (HC) (mean age: 74.9y / Females: 30). Quantitative gait assessments were performed before and after the CSF-TT to identify responders (Resp) and non-responders (nResp). Sulcal morphology was evaluated using MRI, focusing on depth, width, length, and surface area. A generalized linear model (GLM) identified the iNPH sulcal phenotype, and a Support Vector Machine (SVM) classifier was applied to distinguish iNPH patients from controls, as well as Resp from nResp.

Results: The GLM analysis identified sulcal depth and opening as the main features characterizing the iNPH phenotype, with respect to HC. Eight core sulci contributed the most, including compressed central, superior frontal, and frontal intraparietal bilateral sulci, as well as flattened left calcarine and posterior lateral fissures. An SVM classifier trained on these features effectively differentiated iNPH patients from HC (AUC: 0.933) but had limited accuracy for Resp vs. nResp (AUC: 0.556).

Discussion/Conclusion: This study identified an iNPH neuroradiological phenotype based on sulcal morphology, emphasizing depth and opening as key markers. An SVM classifier trained on these features accurately distinguished iNPH patients from HCs but was less effective for Resp vs. nResp. Further studies are needed to explore more advanced sulcal landmarks in iNPH.

## **P17-A: Intravascular lymphoma mimicking inflammatory Cerebral Amyloid Angiopathy**

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### **INTRODUCTION**

We report the case of a patient admitted for new-onset epileptic seizure, secondary to acute cerebral micro- and macro-hemorrhages, with no identifiable predisposing factors.

### **CASE REPORT**

A 74-year-old woman with a history of progressive memory impairment over several months was hospitalized following a generalized epileptic seizure.

Brain MRI revealed subcortical edema, lobar and subarachnoid macro- and micro-hemorrhages, as well as multifocal cortical siderosis. Cerebrospinal fluid (CSF) analysis showed elevated protein levels (1.32 g/L), lymphocytic pleocytosis (16G/L; 62% lymphocytes), and positive Alzheimer's biomarkers (tau: 1700 ng/L, A $\beta$ 42/A $\beta$ 40 ratio: 0.05). Comprehensive immuno-infectious screening and peripheral blood flow cytometry were unremarkable.

Inflammatory cerebral amyloid angiopathy (CAA-ri) was suspected, prompting treatment with methylprednisolone (1 g/day for 3 days, followed by a tapering schedule) and lacosamide (100 mg twice daily). The patient showed initial clinical improvement and was transferred to a rehabilitation unit.

Two weeks later, she experienced a decline in consciousness and developed right-sided hemiparesis. Imaging revealed recurrent left frontal hemorrhage with increased microbleeds. At the family's request, palliative care was initiated, and the patient passed away eight days later. Postmortem examination revealed a high-grade intravascular B-cell lymphoma (IVL) with extensive necrotic-hemorrhagic foci, alongside neuropathological evidence of Alzheimer's disease but no vascular amyloid deposits.

### **DISCUSSION**

While diffuse lobar microbleeds and cortical siderosis are hallmark features of CAA-ri, they can also occur in IVL, making them non-specific findings. IVL can closely mimic the clinico-radiological presentation of microangiopathic disorders due to the presence of malignant cells within small blood vessels, resulting in microvascular dysregulation and disruption of the blood-brain barrier.

### **CONCLUSION**

IVL is a rare and highly morbid condition that remains challenging to diagnose in vivo due to its nonspecific clinical and radiological features. In cases of suspected CAA-ri, a brain biopsy should be considered, as it may be crucial in guiding appropriate treatment strategies.

## **P18-A: Modeling Familial and Sporadic Alzheimer's Disease Using Human iPSC-Derived Neurospheres to Reveal Disease-Specific $\beta$ -Amyloid Pathology and Gene Expression Signatures**

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Neurix SA

Alzheimer's disease (AD) is a complex neurodegenerative disorder characterized by  $\beta$ -amyloid ( $A\beta$ ) accumulation, synaptic dysfunction, and neuronal loss. To better understand the cellular and molecular mechanisms underlying both familial and sporadic forms of AD, we established a human organoid-based disease model using induced pluripotent stem cell (iPSC)-derived neurospheres. This approach enables the study of disease-specific phenotypes in a physiologically relevant, three-dimensional context.

Neurospheres were generated from two complementary sources: (1) familial AD iPSCs harboring APP695 and PSEN1 $\Delta$ E9 mutations, and (2) iPSCs reprogrammed from blood cells of sporadic AD patients with complex genotypic backgrounds. Control neurospheres derived from healthy donors were used for comparison. After 80 days of differentiation, brightfield and fluorescence imaging revealed pronounced  $A\beta$  aggregation in both familial and sporadic AD neurospheres compared to controls, recapitulating hallmark AD pathology *in vitro*.

Quantitative analysis of immunoreactivity demonstrated elevated  $\beta$ -amyloid accumulation in AD-derived neurospheres, with distinct morphological patterns between familial and sporadic models. Gene expression profiling further identified stage-specific dysregulation of neuronal and glial markers, including NeuN (neuronal marker), BRN2 (transient cortical marker), and S100 $\beta$  (astrocytic marker), suggesting impaired neurogenesis and reactive gliosis during early neurodevelopment.

Together, these findings validate our human iPSC-derived neurosphere platform as a robust model for investigating AD pathophysiology. By integrating familial and sporadic genetic backgrounds, this system provides a valuable tool for elucidating disease mechanisms, comparing molecular trajectories, and screening potential therapeutic interventions targeting  $A\beta$  pathology and neuroinflammatory responses.

Our work contributes to bridging the gap between genetic predisposition and disease manifestation, emphasizing the importance of personalized human cell-based models for advancing dementia research and testing new promising drugs.

## P19-A: Modelling (i.e. IHME) or measuring (i.e. SwissDEM) dementia occurrence?

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### Background

The accuracy of the Global Burden of Disease (GBD) estimates and projections for dementia in Switzerland remains uncertain. These modelling methods rely on calibrations derived from the Health and Retirement Study Aging, Demographics, and Memory Study (HRS ADAMS) criteria, which have not been validated in European contexts, including Switzerland. We used empirical data from the SwissDEM epidemiological study to quantify discrepancies between observed dementia prevalence and model-based GBD estimates.

### Methods

SwissDEM is a population-based, one-phase, cross-sectional study that employed standardized protocols developed by the 10/66 Dementia Research Group. Dementia cases were identified using a locally validated version of the 10/66 diagnostic algorithm. Data were collected up to 2022 in community-dwelling and institutionalized older adults in the cantons of Ticino and Zurich. We compared SwissDEM with GBD estimates using demographic data of the Swiss national census.

### Results

Despite participation rates below 50%, socio-demographic characteristics of the SwissDEM sample closely matched national data, suggesting high representativeness and good generalizability. In 2022, the SwissDEM study estimated 163,474 dementia cases among older adults in Switzerland—approximately 20,000 more than the GBD 2019 estimate (142,105; 95% UI: 121,551–164,647). Differences were especially pronounced among the oldest age groups (>85 years).

### Conclusion

Empirical assessments in population representative samples provide dementia prevalence estimates that are more accurate than those of indirect modelling approaches like the GBD. The GBD approach likely underestimates actual dementia prevalence, particularly in nursing homes, and by missing milder cases among octogenarians and nonagenarians. Our findings underscore the necessity of robust epidemiological studies to accurately measure and monitor the true dementia burden, ensuring informed public health planning and intervention strategies.

## **P20-A: Multicenter Evaluation of the NeuroLF Brain PET System: Initial Real-World and Clinical Trial Data**

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**Introduction:** The logistical and financial burdens of conventional full-body PET scanners limit patient access and operational efficiency in neuroimaging. This work demonstrates Real-World and Clinical Trial Data assessment of NeuroLF, a compact, brain-dedicated PET system designed to overcome these barriers. NeuroLF designed to reduce the system's footprint, cost, and infrastructure requirements, enabling flexible, high-throughput deployment in diverse clinical environments.

**Methods & Data Sources:** We present a consolidated analysis of the NeuroLF's clinical performance, drawing from two principal sources. Firstly, under a clinical research agreement with ProScan Imaging (Naples, FL, USA), the system is being utilized in routine diagnostic practice. Demonstrating its capacity for high-throughput operation, over 150 patient scans were performed within the first three months post-installation. For this conference, we present an interim analysis of a representative cohort of approximately 10 patients who were imaged with amyloid tracers (mainly Vizamy). Secondly, we present initial data from the ExploreBPET study, an ongoing, explorative, multicenter clinical trial evaluating the NeuroLF system in Leipzig and Zurich. This trial is enrolling patients utilizing a range of tracers including FDG, FET, and agents for tau and amyloid pathology.

**Preliminary Results:** Data from both the real-world clinical setting in Naples and the formal ExploreBPET trial will be presented. The analysis focuses on diagnostic comparisons, image quality, and operational metrics in a high-volume workflows. The results demonstrate robust system performance and consistent, high-quality imaging across different tracers and international sites.

**Conclusion:** This multicenter, real-world evidence demonstrates the successful clinical implementation and versatility of the NeuroLF system. The data confirm its suitability for both routine diagnostic use in a high-throughput commercial imaging center and for advanced research applications within a formal, multicenter trial. The NeuroLF system represents a validated and robust solution for expanding patient access to essential neurological PET imaging.

## P21-A: Plasma Biomarkers and Comorbidity-Driven Cognitive Decline: Insights from the A4B Community-Based Dementia Cohort in Sub-Saharan Africa

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The approval of anti-amyloid therapies for early Alzheimer's disease (AD) in Europe has renewed hope for patients but also highlights persistent global disparities in diagnosis. As the 2024 revised AD criteria shift toward a clinico-biological definition of AD (IWG 2024), their application across diverse settings, particularly in sub-Saharan Africa, raises critical concerns. Limited access to diagnostic infrastructure (PET, MRI), the high prevalence of comorbidities (e.g., hypertension, diabetes, infections), and co-pathologies (e.g., vascular, synuclein, mixed dementias) can influence both the clinical expression and biological interpretation of biomarkers. In this context, validating plasma biomarkers within real-world, community-based African populations becomes crucial. This study analyzes 51 participants from the A4B cohort at Yaoundé General Hospital (mean age  $61.6 \pm 7.5$  years; 56.9% female; mean education  $11.3 \pm 2.6$  years). Clinical stages included cognitively unimpaired (27.5%), mild cognitive impairment (43.1%), and dementia (29.4%). Hypertension (21.6%), diabetes (5.9%), and multimorbidities (9.8%) were the most common comorbidities. Cognitive assessments showed a mean CDR of  $0.44 \pm 0.38$ , AVQ of  $5.65 \pm 0.98$ , and QPC of  $5.86 \pm 2.79$ . Biomarker analyses suggest that plasma P-Tau217 and NfL can discriminate between stages of cognitive impairment (dementia vs MCI/unimpaired), while GFAP expression trends to appear modulated by specific comorbidities, notably hypertension. APOE genotyping indicates a presence of  $\epsilon 4$  alleles in the cohort, with variable distribution regarding heterozygotes, suggesting potential protective or modulatory genetic factors in this population. These early insights underscore the relevance of plasma biomarkers, in the context of prevalent cofactors and genetic profiling, for dementia staging in diverse biological contexts such as sub-Saharan Africa. They also highlight the critical need for inclusive, population-specific data for AD biomarker development and contextualized research. Expanding research efforts to multicentric, large-scale cohorts and investigating the impact of ethnicity and comorbidities could provide essential advances for refining Alzheimer's disease biomarker frameworks worldwide.

## **P22-A: Quantitative assessment of I-123-ioflupane uptake using absolute and relative SUV in the diagnosis of dementia with Lewy bodies**

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### **Background:**

Quantification of I-123-ioflupane uptake using modern SPECT/CT improves diagnostic accuracy for disorders affecting the nigrostriatal pathway. This study assessed whether absolute and relative standardized uptake values (SUV) could distinguish dementia with Lewy bodies (DLB) from non-DLB in patients with suspected DLB and explored associations with core clinical features, including visual hallucinations (VH) and REM sleep behavior disorder (RBD).

### **Methods:**

Seventy-four patients (mean age  $71.5 \pm 9.26$  years; 39% female) were retrospectively included. All underwent I-123-ioflupane DAT-SPECT with both iterative (Flash 3D) and quantitative reconstructions. SUV<sub>max</sub>, SUV<sub>mean</sub>, and relative SUV (rSUV) values were extracted for the caudate, putamen, and striatum. Uptake metrics were compared between DLB and non-DLB groups and analyzed in relation to clinical features, including visual hallucinations (VH) and REM sleep behavior disorder (RBD).

### **Results:**

Visual assessment classified 28/74 scans (38%) as abnormal (sensitivity 90%, specificity 80%, AUC 0.846). Quantitative SUV<sub>max</sub> in the striatum and putamen showed the highest diagnostic performance (AUC up to 0.83). Striatal SUV<sub>max</sub> remained an independent predictor of DLB in multivariable analysis (OR = 0.58,  $p = 0.003$ ). Patients with VH had significantly lower striatal SUV<sub>max</sub> than those without ( $p = 0.004$ ), with an optimal cutoff of  $\leq 6.0$ g/mL (AUC = 0.70, sensitivity 64.3%, specificity 80.4%). No significant differences were observed for RBD.

### **Conclusions:**

Quantitative I-123-ioflupane uptake assessment using SUV measures offers clinically relevant diagnostic value for differentiating DLB from other neurodegenerative diseases. It also helps in identifying patients with visual hallucinations, supporting the broader integration of SUV-based dopaminergic imaging into clinical workflows.

**P23-A: Reduced levels of the sigma-1 receptor in the brains of Alzheimer's disease patients: associations with synaptic loss, amyloid-beta and tau**

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**Background:** The sigma-1 receptor ( $\sigma$ 1R) has emerged as a critical player in Alzheimer's disease (AD), serving as both a potential biomarker and a therapeutic target. This study aimed to investigate alterations in regional  $\sigma$ 1R expression in relation to amyloid-beta and tau pathologies, synaptic loss, gliosis, and autophagy in the brains of patients with AD and animal models.

**Methods:** Immunohistochemical staining for  $\sigma$ 1R, LC3b, GABARAP, and LAMP1 was conducted on postmortem tissue slices from frontal, temporal, and entorhinal cortices and the hippocampus from 44 AD patients and 45 nondemented controls (NCs) from the brains of P301L tau, APPPS1 and arcAb amyloidosis mice. Proteomics, single-cell RNA analysis and transcriptomics were performed on the brains of APP/PS1 mice. Relationships between  $\sigma$ 1R expression and the levels of amyloid-b, phospho-tau, synaptic density markers, and astrocytic and microglial markers were examined.

**Results:** Compared with that in the NC group, the level of  $\sigma$ 1R expression in the hippocampus and frontal cortex but not in the entorhinal or temporal cortices in the AD group was lower.  $\sigma$ 1R levels were negatively correlated with amyloid-beta, phospho-tau, and Braak stages but positively correlated with synaptic density (SV2A and synaptophysin), GFAP and Iba1. The colocalization of  $\sigma$ 1R with AT-8 and the autophagy markers LC3b, GABARAP, and LAMP1 was observed in the brains of P301L mice and AD patients. Reduced  $\sigma$ 1R expression and SIGMAR1 level was observed in the hippocampus of APP/PS1.

**Conclusions:** Our findings provide postmortem evidence of reduced  $\sigma$ 1R expression in the frontal cortex and hippocampus of AD patients and in APPPS1 mice. Furthermore,  $\sigma$ 1R expression is negatively correlated with the levels of amyloid-beta and phospho-tau but positively correlated with the levels of the synaptic markers GFAP and Iba1, highlights its importance and potential as a biomarker and therapeutic target in AD.

## P24-A: ROMENS: An Automated Regional Real-World Data Registry for Dementia Research and Clinical Care in Western Switzerland

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**Background:** Biologics for Alzheimer's disease (AD) demand real-world data (RWD) infrastructures to assess safety, effectiveness, and system-level impact. The ROMENS registry was developed to address fragmented data collection across memory clinics in French-speaking Switzerland.

**Objective:** To establish a scalable, multi-center registry for RWD collection on AD biologics and supporting clinical and policy decision-making.

**Methods:** Eight memory clinics participate in ROMENS, under cantonal ethics approvals. A working group of clinicians and researchers defined core variables aligned with ALZ-NET and InRAD, supported by a unified ROMENS Dictionary. An automated pipeline—built with SQL and Python—extracts structured data from Electronic Patient Records (EPRs) and uploads them into REDCap. A real-time dashboard, developed in Python using Dash, enables flexible cohort definition using an unlimited number of combinable filters (via intersection or union logic), supporting both exploratory and hypothesis-driven research.

**Results:** ROMENS collects a 37-variable Minimum Dataset and over 200 Extended Dataset variables across key domains: demographics, diagnostics, neuropsychology, medication use, and safety events (SAEs, ARIA). It currently includes 8,712 patients across 8 clinics. The dashboard facilitates customized cohort selection with user-defined inclusion/exclusion criteria.

**Conclusion:** ROMENS provides a replicable model for embedding automated RWD collection into routine dementia care. By integrating with EPRs and enabling flexible data access, it supports longitudinal tracking and real-world evaluation of AD therapies. The geographical scope of the system is presently confined to the Romandie region, and the quality of the data is commensurate with the consistency of the EPR systems that are contributing to it.

**Data Deposition:** ROMENS data are governed by the consortium. Access is subject to ethical approval and data use agreements."

## **P25-A: Screening of Alzheimer's Disease Using an AI-Driven Platform: Study Design and Preliminary Results from the Geneva Site of the PREDICTOM Study**

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**Background:** The early prediction of Alzheimer's disease (AD) represents a pressing public health priority. Although population-wide screening programs are well established in fields such as oncology and cardiovascular medicine, a comparable standardized approach for dementia screening is still lacking. To address this gap, the PREDICTOM project was initiated to develop and validate an artificial intelligence (AI)-driven screening platform aimed at the early detection and prediction of AD.

**Method:** PREDICTOM is an observational, prospective cohort study conducted across seven European centers, including Geneva (Switzerland), and launched in April 2025. In this poster, we present the specific implementation of the study at the Geneva site, including the recruitment strategy and preliminary data. Recruitment in Geneva focuses on the Swiss Brain Health Registry, a platform designed to people who wish to contribute to research on Alzheimer's disease. The preliminary data correspond to Level 1, the initial stage of the screening process, which consists of a fully home-based assessment. This includes digital biomarkers (cognitive tasks, hearing tests, eye-tracking via webcam, and self-administered questionnaires) as well as physiological biomarkers (finger-prick blood sampling and saliva collection kits).

**Results:** The interim analysis of Level 1 data will include approximately 100 participants.

**Conclusions:** The PREDICTOM study aims to deliver novel insights into the diagnostic accuracy of home-based digital and physiological measures for the early detection of Alzheimer's disease. At the Geneva site, the preliminary data highlight the feasibility and acceptability of remote assessments in a digital screening platform for AD. A comprehensive analysis of data from the first 100 participants from Geneva, will be presented at the Swiss Dementia Forum 2025.

## **P26-A: The OMICS-AD multimodal biomarker cohort study: design, methods, and cohort characteristics**

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### **BACKGROUND**

Multiple pathophysiological processes have been described in Alzheimer's disease (AD). Their inter-individual variations, complex interrelations, and relevance for clinical manifestation and disease progression remain poorly understood. The Omics-AD study's main scope is to perform an in-depth multi-modal characterization in people with pre-clinical and early AD to a) better understand pathophysiological changes of AD and b) identify and validate new biomarkers for AD and AD-related outcomes, including cognitive decline and neuropsychiatric symptoms (NPS).

### **METHOD**

Memory-clinic patients and volunteers had been included in a prospective brain aging study at four Swiss memory clinics. Comprehensive clinical and neuropsychological data was collected using validated instruments at baseline and follow-up visits. Paired blood and CSF samples along with structural MRI were obtained at baseline. CSF markers of the core AD pathology have been used to determine the presence of AD pathology. Untargeted omics and targeted molecular analysis will be performed and integrated in multi-modal, multi-omics data analysis.

### **RESULT**

A total of 434 participants were included by December 2024. Of these, 200 (46.1%) were cognitively unimpaired (of which 80 had subjective cognitive decline, SCD) and 234 (53.9%) were cognitively impaired (203 with mild cognitive impairment, MCI, and 31 with mild AD dementia). Half of the participants presented with NPS as measured by the Neuropsychiatric Inventory Questionnaire, while the most common symptoms were irritability (19%) and depression (18%). In total, 45.6% (n = 173) subjects were amyloid positive (25.7% of NC, 23.2% of SCD, 61.7% of MCI, and 75.9% of mild AD dementia).

### **CONCLUSION**

This brain aging, multi-centric, and well characterised cohort unique in Switzerland will allow for single- and multi-omics analysis, to investigate in depth molecular and biological pathway alterations, and their relations with clinical manifestation and progression. It will further serve for the validation of new biomarkers to diagnose and monitor relevant disease processes.

## P27-A: The quest for the best: manual, atlas- and spatial prior-based detection of locus coeruleus

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Despite advances in neuromelanin-sensitive brain imaging combined with a plethora of software solutions, the robust and reliable non-invasive detection of the locus coeruleus (LC) in the human brain stem remains challenging. In the absence of ground truth, current methodological developments cover the wide span between manual labelling, atlas- and signal intensity-based approaches. We sought to evaluate the spatial accuracy and consistency of atlas- and probabilistic spatial prior-based LC detection on the background of manual labelling. We acquired neuromelanin-sensitive magnetic resonance imaging data in healthy volunteers ( $n = 24$ ; mean age 40 years; 42% females). Manual labelling by 9 raters performed twice provided the basis for individual- and group-level comparisons with the automated detection methods. For the atlas-based labelling, we tested separately seven open-access LC atlases, the averaged output of the manual labelling, and a consensus reference representing the atlases' overlap. Each one of the atlases served as spatial prior for automated LC detection in a probabilistic segmentation framework. Manual labelling showed moderate inter-rater agreement (mean Dice = 0.7), with higher detection variability in the rostral and caudal LC. Atlas-based labelling demonstrated a low spatial concordance for all open-access atlases (Dice = 0.3–0.4) in native space with inconsistent boundary accuracy and volume similarity relative to the consensus reference. In the same comparison, the averaged manual labelling atlas showed higher spatial overlap (Dice = 0.6). LC detection using spatial priors achieved the highest voxel-wise correlations ( $r = 0.3$ ) when using the averaged manual labelling atlas as prior. Principal component analysis confirmed greater spatial compactness for atlas-based labelling in comparison with spatial prior-based detection, underscoring method-dependent differences in anatomical organization. Our results highlight the potential advantage of atlas-based labelling for robust and spatially reliable LC identification. Observed variability across methods and atlases underscores the need for harmonized validation strategies and context-sensitive approaches to improve reliability.

## P28-A Uncover Lewy Body Disease with Neurotechnology

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Introduction: Lewy body disease (DLB) is the second most common cause of neurodegenerative dementia. Early identification of individuals at risk for DLB is crucial to maximize the efficacy of neuroprotective interventions. Hallucinations are early and key symptoms of DLB and previous research, particularly from studies in Parkinson's disease, suggests they may be associated with cognitive decline.

Aim: We aimed at investigating neural correlates of hallucinations in DLB, their characteristics and evolution, as well as their link with cognitive impairment and decline.

Method: A literature search was conducted using Ovid MEDLINE, resulting in the inclusion of 42 studies. All studies investigated minor or complex hallucinations in DLB patients, using fMRI, PET, DAT or EEG imaging.

Results: Hallucinations in DLB are associated with complex large-scale network alterations, involving visual, attentional, memory-related, default mode and salience networks. Most studies reported reduced functional connectivity both within and between networks. However, the role of striatal dopamine uptake, as assessed by DAT imaging was inconsistent. Hallucinations were typically evaluated using brief questionnaires, while some studies provided valuable insights into their characteristics. Direct comparisons between DLB patients with and without hallucinations remain limited, however the available studies offer support for a distinct clinical profile. Several findings suggest a possible association between neural basis of hallucinations and cognition. These results underscore the need for more detailed and longitudinal investigations.

Perspectives: Further studies investigating hallucinations as a new biomarker are needed to foster early and differential diagnosis, as well as improve prognosis of cognitive decline. To address these gaps, we have recently initiated a 5-year longitudinal study including 40 DLB patients, 40 non amnesic MCI and 40 healthy controls. Our study focuses fMRI and EEG imaging, includes diverse neuropsychiatric and neuropsychological assessments, as well as a robotic paradigm to induce presence hallucinations in a controlled setting.

**P29-B: Altered Excitation/Inhibition in the Prefrontal Cortex of Alzheimer's Disease Mouse Model During REM sleep**

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The intricate relationship between Alzheimer's Disease (AD) and sleep is bidirectional since sleep disturbances are increasingly recognized as both potential markers of AD and factors that may exacerbate the disease progression. In particular, reduced rapid eye movement (REM, also called paradoxical) sleep in individuals with AD is thought to contribute to cognitive decline and the AD progression. Recently, we have identified a somatodendritic decoupling in the dorsal prefrontal cortex (dPFC) during REM sleep supporting synaptic plasticity and emotional memory consolidation. We hypothesized that disruptions in this mechanism may contribute to AD-associated cognitive impairments. To investigate this, we characterized the dPFC somatodendritic decoupling in AD mice models across the sleep-wake cycle using simultaneous 2-photon calcium imaging and electrophysiological recordings in head-restrained, spontaneously sleeping mice. We found a complete absence of dPFC somatodendritic decoupling during REM sleep in 8-13 months old 5xFAD mice, primarily due to decreased dendritic activity of pyramidal (PYR) cells. Notably, age-dependent differences emerged with 5xFAD mice older than 1 year showing increased PYR somatic and dendritic activity during REM sleep compared to younger mice, possibly reflecting compensatory mechanisms for REM sleep deficits. Interestingly, a similar trend was observed in the PYR somatic activity of 5xFAD wild-type animals older than 1 year but not in 3-month-old BL6 mice, suggesting an age-related, AD-independent decrease in activity during non-REM (NREM) sleep. While the underlying mechanisms remain unclear, we propose that REM sleep-specific restoration of the dPFC somatodendritic decoupling could serve as a potential target for improving memory functions in AD.

## P30-B: Astrocytic SHANK3 loss as an early driver of striatal circuit failure in Huntington's disease

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Huntington's disease (HD) has long been framed as a neuron-centric disorder, yet evidence points to early astrocyte dysfunction at disease onset. In the striatum, where astrocytes maintain ion and neurotransmitter homeostasis for populations of medium spiny neurons (MSNs), both HD patient-tissue and mouse models reveal impairments in GPCR-mediated Ca<sup>2+</sup> signaling, glutamate and K<sup>+</sup> clearance, and metabolic support (Khakh et al. 2017). An astrocyte-specific study across two HD mouse models (R6/2 and Q175), together with post-mortem human striatal RNA-seq, identified a conserved core set of transcripts altered in both species; 97% were downregulated, including genes for Ca<sup>2+</sup> signaling, GPCR signaling, and scaffolding proteins such as SHANK3 (Diaz-Castro et al. 2019 ; Ollivier et al. 2024). These reductions emerge at early stages, before astrocyte loss or astrogliosis. We hypothesize that loss of SHANK3 in astrocytes destabilizes their homeostatic programs (Zehnder et al. 2021), rendering both astrocytes and neurons vulnerable. At presymptomatic stages, astrocytic dysfunction may remain silent, but subsequent neuronal stressors could tip the system into imbalance, leading to MSN apoptosis and circuit breakdown. To test this hypothesis, we generated a transgenic mouse model with striatal astrocytic SHANK3 deletion. Single-cell RNA-sequencing revealed strong overlap with transcriptional signatures from HD, including downregulation of genes involved in glutamate uptake (Slc1a2/GLT1), K<sup>+</sup> buffering (Kcnj10/Kir4.1), mitochondrial metabolism, Ca<sup>2+</sup> signaling, and HD-associated proteins (HAP1). Consistently, histological analyses showed reduced neuronal density, with DARPP-32 and cleaved caspase-3 co-localization confirming apoptotic death of MSNs. Astrocytes displayed mitochondrial abnormalities, including reduced content and increased spherical morphology, indicating impaired bioenergetic support. This neuronal degeneration was accompanied by behavioral changes, including excessive grooming and motor deficits. Together, these findings support that astrocytic SHANK3 loss destabilizes metabolic and homeostatic programs, weakens striatal networks, and increases MSN vulnerability well before neurodegeneration. Ongoing work will test whether restoring SHANK3-dependent pathways, or enhancing astrocytic mitochondrial competence, can ameliorate cognitive and motor deficits associated with HD.

## P31-B: Brain apoE particle composition defines its functions

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Alzheimer's disease (AD) is the leading cause of dementia in elderly adults, with 55 million cases recorded worldwide in 2019. Genetic variations of apolipoprotein E (APOE) affect the risk of AD development, with the APOE4 allele being detrimental, APOE3 neutral, and APOE2 protective. Yet, the relationship between APOE genotype, apoE particle composition, and apoE function in AD remains elusive.

Previous studies indicated that the role of apoE in the brain depends on particles' cellular origin. Notably, the composition of apoE particles is also cell-type-specific, with pericyte-secreted apoE containing more cholesterol than astrocyte-secreted apoE. This creates a challenge for studying the roles of different apoE isoforms in AD pathogenesis.

We propose a genotype- and cell-type-specific approach to investigate the composition and function of apoE particles. We hypothesize that both the APOE genotype and cell type of origin influence the lipid and protein composition of apoE particles, which in turn modulates their role in AD pathology.

To test our hypothesis, we have differentiated the apoE-secreting cells of the brain: astrocytes, pericytes, and microglia from human induced pluripotent stem cells (iPSCs). By including apoE-secreting cells with different APOE genotypes (derived from isogenic iPSCs), we will investigate the influence of genetic variants on apoE particle composition in a cell-type-specific manner. We will investigate the protein and lipid compositions of apoE particles secreted by each differently genotyped cell type using liquid chromatography-mass spectrometry (LC-MS). Next, we will assess the role of these particles in AD by characterizing their effect on amyloid beta and tau accumulation in neurons.

By the end of our project, we aim to answer key questions: how the composition of apoE particles is linked to the cell type of origin and APOE genotype, and how these particles affect cerebrovascular health in the context of AD.

## P32-B: Cerebral Small Vessel Disease in Early vs Late Onset Alzheimer's Disease

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### Introduction

Cerebral small vessel disease (CSVD), including hypertensive arteriopathy (HTNA) or cerebral amyloid angiopathy (CAA), is a frequent co-morbidity in patients with Alzheimer's disease (AD). As CSVD prevalence increases with age, it might differently affect patients with early-onset Alzheimer's disease (EOAD) or late-onset Alzheimer's disease (LOAD). Here, we tested whether CSVD features differ by age at symptom onset within AD.

### Methods

We retrospectively included 126 AD patients (CSF or amyloid-PET positive) evaluated at the Leenaards Memory Center (Lausanne University Hospital – CHUV). Forty patients were defined as EOAD (mean age=59.3±4.19, 57.5% females) and 86 patients as LOAD (mean age=72.8±4.36, 59.3% females). Variables included demographics, clinical, vascular risk factors, MRI markers of CSVD rated according to established guidelines, and the presence of HTNA and CAA. Groups were compared using parametric or non-parametric tests, as appropriate.

### Results

Groups were similar in cognitive performance (MoCA EOAD 19.67±5.68; LOAD 18.69±5.49;  $p=0.434$ ). Patients with LOAD had a higher rate of hypertension and diabetes ( $p=.002$  and  $p=.033$ , respectively). Across CSVD MRI markers, white matter hyperintensities and perivascular spaces burden were greater in LOAD ( $p<.005$ ), whereas cortical siderosis, lacunes, and microbleeds showed no significant group differences. HTNA score was higher in LOAD (median [IQR] 1 [0–2] vs 0 [0–1],  $p<.001$ ) while the proportion with moderate/severe HTNA (score  $\geq 2$ ) did not differ significantly. The prevalence of probable CAA was 31.4% in LOAD versus 17.5% in EOAD ( $p=.102$ ); any CAA (possible or probable) was more frequent in LOAD ( $p<.001$ ).

### Conclusion

Within an AD cohort from a memory center, LOAD is associated with a heavier vascular risk profile and CSVD burden. While HTNA and any CAA were greater in LOAD, the occurrence of probable CAA was similar in EOAD and LOAD. These findings highlight the importance of evaluating vascular co-pathology even in EOAD, to clarify potential age-related pathogenic differences.

### **P33-B: Characterization of brain barrier fluorescent reporter mouse models of cerebral amyloid angiopathy**

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There has been a renewed focus on the role of central nervous system (CNS) fluids and barriers in neurological disorders such as cerebral amyloid angiopathy (CAA). A body of suggestive evidence has indicated a link between impaired amyloid- $\beta$  ( $A\beta$ ) clearance and CAA formation, highlighting a fundamental need to improve our insights into the mechanisms of brain clearance. Nonetheless, the mechanisms for fluid circulation and solute exchange in the brain parenchyma remain highly debated and poorly understood. In many studies, full consideration of the brain barriers that compartmentalize the CNS is lacking. With this project, we aim to provide new transgenic mouse models marking the brain barriers that will help us to fill these critical knowledge gaps between CNS fluid clearance and CAA progression. Two novel specific dual-reporter mouse strains: one visualizing CNS vasculature using Claudin5-GFP (cerebral blood vessels) and Prox1-TdTom (lymphatic vessels) and one marking the brain borders with Aqp4-mRuby3 (for astrocyte endfeet of the glia limitans) and VE-cadherin-GFP (for the leptomeninges and blood vessels), were successfully crossed with an ArcA $\beta$  transgenic mouse line, which has resulted in two novel triple-transgenic models of cerebral amyloidosis. In the first stage, A $\beta$  deposition was observed in correlation with changes of brain barrier marker fluorescent expression using ex vivo imaging on decalcified skull or fixed brain sections at different ages (early vs chronic stage of disease). Secondly, solute drainage pathways from the interstitial fluid space were investigated through evaluation of tracer distribution at various timepoints after infusion into different brain regions and the CSF space. Our preliminary results demonstrate that our novel brain barrier reporter mice enable new perspectives on the understanding of brain clearance in rodent CAA models. Going forward, our histological findings will be validated with multiple in vivo imaging modalities, including two-photon microscopy and synchrotron-based X-ray imaging.

## **P34-B: Dissecting the role of microglial TDP-43 in demyelination and lipid handling**

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TDP-43 is a DNA-RNA binding protein encoded by the TARDBP, and it is ubiquitously expressed by all cell types. Cytoplasmic TDP-43 aggregates are hallmarks for Amyotrophic Lateral Sclerosis (ALS) and a subset of frontotemporal lobar degeneration (FTLD). TDP-43 aggregates are also found in Alzheimer's disease (AD) cases, mainly in association with the genetic risk factor apolipoprotein E4 (APOE4), suggesting a link between TDP-43 and lipid metabolism. Microglia, the innate immune cells of the central nervous system, are emerging key players in the pathogenesis of several neurodegenerative diseases. These professional phagocytes continuously survey the brain parenchyma, maintaining tissue homeostasis throughout life.

While TDP-43 dysfunction in brain diseases has been ascribed primarily to neurons, growing evidence implicates also glial cells, including astrocytes, oligodendrocytes and microglia. However, the role of TDP-43 in regulating microglial function, and in particular, its specific role in controlling lipid metabolism remain unexplored.

Using a microglial conditional knockout (cKO) mouse model, we discovered that microglia lacking TDP-43 exhibit deficits in lipid handling during brain development. RNA-sequencing of acutely sorted microglia further revealed alterations in lipid-related genes, including low-density lipoprotein receptor (LDLR) and acetyl-CoA acetyltransferase1 (ACAT1), which converts cholesterol to cholesteryl ester, suggesting potential impairment in microglial lipid metabolism. This prompted us to investigate whether TDP-43 would modulate microglial response following demyelination.

We used lysophosphatidylcholine (LPC) stereotaxic injection in the corpus callosum of control and TDP-43 cKO adult mice to induce focal demyelination. When analyzed 14 days post-injection, cKO mice displayed an increased lesion size, associated with abnormal accumulation of CD68-positive phagolysosomes. Additionally, loss of microglial TDP-43 led to a significant increase in lipid droplets in the demyelinated area. These results so far suggest that microglia lacking TDP-43 are defective in scavenging and handling myelin debris following demyelination, thus impairing the remyelination process.

### **P35-B: Electrophysiological markers of network communication in an Alzheimer's disease mouse model with early tau pathology**

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The aggregation of misfolded tau protein in the brain is a critical step in the development of neurodegenerative tauopathies, such as Alzheimer's disease and frontotemporal dementias. The extent and severity of tau pathology correlate with cognitive decline, but the cellular and network mediators of memory consolidation deficits have not yet been elucidated. Tauopathy mouse models have historically exhibited rapid, non-physiological and widespread transgenic overexpression of mutant tau, and so the network effects of early and localised tau pathology that exists at disease onset remain largely unexplored. We employed a novel tau mouse model, the MAPTS305N; Int10+3 knock in (MAPT KI) line, to investigate the earliest stages of tau pathology, capturing electrophysiological changes using concurrent Neuropixels recordings across distributed brain regions, over the course of tau pathology progression.

Electrophysiological deficits became more pronounced with age and pathological advancement. The entorhinal cortex and hippocampal CA1 exhibited increased neuronal firing across behavioural states, in contrast to previous observations in transgenic models. Sleep macrostructure was also disordered, showing an increase in REM sleep and fragmentation of nREM sleep. During nREM sleep, oscillatory events involved in coordinating multiple brain regions for memory consolidation were impaired in older MAPT KI mice. Specifically, spiking responses to sleep spindles, and the temporal coordination of spindles to hippocampal ripples and cortical delta waves became dysregulated in older MAPT KI mice. This work characterises the early network effects of tau pathology, revealing deficits in processes integral to memory consolidation. These findings may provide novel targets for the direct treatment of network dysfunction in tauopathies. Additionally, these circuit deficits may be detectable in patients, and represent novel potential biomarkers for the early detection and diagnosis of tau-related neurodegenerative disease.

## P36-B: From Liver to Brain: How Hepatic Dysfunction Fuels Neurodegeneration

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**Background:** Increasing evidence suggests that liver dysfunction may contribute to Alzheimer's disease (AD) pathogenesis. Although type C hepatic encephalopathy (HE) is associated with cognitive impairments, particularly in attention and memory, the potential overlap with AD remains largely unexplored. While studies have confirmed a link between cirrhosis and cognitive decline, the role of the gut-liver-brain axis in neurodegeneration has only recently regained scientific attention, highlighting the importance of liver health for central nervous system function. However, the underlying mechanisms remain poorly understood.

**Objective:** To investigate the potential connection between liver failure and the development or progression of Alzheimer's disease.

**Methods:** Chronic liver disease (CLD) was induced in rats via bile duct ligation (BDL). Alzheimer's pathology was assessed through Congo red staining for amyloid beta (A $\beta$ ) and Gallyas staining for tau. Immunohistochemistry was used to evaluate changes in aquaporin (water) channels (Aqp1, Aqp4, Aqp9) and glial fibrillary acidic protein (GFAP) expression. Blood levels of neurodegeneration markers (neurofilament light chain (NfL), A $\beta$ , p-tau, t-tau, GFAP, and myelin oligodendrocyte glycoprotein (MOG)) and bile acids were measured and compared between BDL and SHAM-operated control rats.

**Results:** BDL rats exhibited hallmark AD pathology, including intracellular A $\beta$  deposition and tau abnormalities characteristic of pre-tangle and neurofibrillary tangle (NFT) stages. These changes were accompanied by dysregulation of brain water channels and significant alterations in circulating neurodegeneration biomarkers and bile acid profiles compared to SHAM controls.

**Conclusion:** Our findings highlight the importance of liver health for central nervous system function and suggest a contributory role in cognitive decline, potentially increasing the risk of Alzheimer's disease. These results support the integration of liver function assessment into the diagnostic process for dementia and underscore the importance of a systemic approach to understanding AD pathogenesis.

## **P37-B: Generation of Seed-Independent, Reversible $\beta$ -Sheeted Tau Aggregation in an Inducible H4 Cell Line**

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The aggregation of Tau protein is a hallmark of several neurodegenerative diseases including Alzheimer's disease (AD). Most current Tau aggregation models require an inducer (seeds or small molecules) to promote aggregation. Here, we generated a novel H4 cell model of tauopathy expressing the 1N4R isoform of Tau with the frontotemporal dementia (FTD) mutation P301L and Pick's disease mutation S320F (Tau1N4R-DM) in a regulatable fashion (tet-on).

Expression, hyperphosphorylation, oligomerization and aggregation of Tau1N4R-DM over time was investigated using various biochemical (Western & dot blotting, sarkosyl extraction, HTRF) and immunocytochemistry assays. The status of hyperphosphorylation and filament formation was analyzed by phosphoproteomics and electron microscopy, respectively. Cytotoxicity was addressed by MTT and LDH assay.

Upon doxycycline induction, the Tau expression reaches saturation at 24 h. Tau1N4R-DM is hyperphosphorylated at 53 sites, similar to the phosphorylation status of Tau in the AD brain. We found that Tau1N4R-DM is highly amyloidogenic and forms sarkosyl insoluble  $\beta$ -sheeted fibrous aggregates in H4 cells. Switching off the expression of Tau inhibits Tau expression and clears the pre-formed Tau aggregates within five days. Surprisingly, the aggregation of Tau1N4R-DM does not affect the viability of the cells.

The Tau1N4R-DM H4 cell model forms fibrous aggregates without the need for external inducers. It can be tested for screening of Tau aggregation modulators, making it a suitable model for studying Tau pathology and potential therapeutic interventions.

## **P38-B: Light mediated CDK5 repression and its potential effects on the circadian clock and Alzheimer's disease**

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Cyclin-dependent kinase 5 (Cdk5) is a proline-directed serine/threonine protein kinase that plays a vital role in the cell cycle and the central nervous system. Cdk5 is controlled by neuron-specific activators p35 and p39 and it becomes active upon direct binding, forming a heterodimer complex. Cdk5 has emerged as a key mediator in Tau phosphorylation and its hyperactivation promotes the amyloid plaque formation that leads to Alzheimer's disease. Moreover, Cdk5 regulates the mammalian circadian clock by phosphorylating key clock components such as CLOCK and PER2, and recent studies have shown that its activity is downregulated by light. In this study, we focus on the repression of the Cdk5 by light and more specifically, we aim to identify the light modification site that is responsible for the Cdk5 activity. For this reason, we test various mutations on the identified phosphorylation sites that would have an effect on the activity of the Cdk5. For the in vitro studies we are using forskolin as a light mimic in NIH 3T3 fibroblast mouse cells which have been transfected with the Cdk5 mutants.

## P39-B: Linking Brain Networks to Tau Propagation in Alzheimer's Disease

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Alzheimer's disease is characterized by progressive amyloidopathy and tauopathy. Recent evidence highlights greater-than-expected inter-individual variability in tau accumulation patterns across brain regions, closely reflecting clinical heterogeneity. However, the mechanisms underlying tauopathy spread remain poorly understood. A leading hypothesis posits that neural connections serve as conduits for the spread of aggregated tau across brain regions, with neural activity exacerbating tau release and spreading. Variability in white matter connections (structural connectivity) and neural activity synchronization (functional connectivity) may therefore contribute to differences in tau accumulation and clinical progression across individuals.

In this study, we used multimodal brain imaging and advanced analytical methods to investigate whether tau spreading is driven by structural connectivity, functional connectivity, or their combination. We conducted a cross-sectional analysis of 198 Memory Clinic patients ( $71.5 \pm 7.7$ yo; 101 females) assessed at the Memory Center of Geneva University Hospitals. Participants underwent amyloid-PET, tau-PET, magnetic resonance imaging, and neuropsychological evaluation. Reference structural, functional, and partialized functional connectivity—a measure reflecting functional synchronization through monosynaptic structural pathways—were derived from 100 healthy subjects from the Human Connectome Project. Using graph signal processing tools, an emerging area in neuroscience research, we assessed the similarity between regional tau accumulation and the underlying brain connectivity networks. At the group level, we found that tau distribution closely followed structure-function connectivity patterns, particularly as summarized by partialized functional connectivity. At the individual level, a score quantifying tau spreading through the structure-function brain network was associated with Braak stage and with cognitive impairment, in both amyloid-positive and cognitively impaired amyloid-negative individuals.

These findings from a Memory Clinic cohort support the hypothesis that tau spreading is mediated by both structural and functional brain connectivity. Anticipating the pathways of tau spreading could inform patients and caregivers about the likely clinical progression and support the development of personalized interventions.

## **P40-B: Longitudinal cardiovascular risks and their impact on white matter hyperintensities**

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**Introduction:** Cerebral small vessel disease, a major contributor to stroke and cognitive decline with aging, commonly appears as white matter hyperintensities (WMH) on MRI. WMHs vary in location and microstructure, reflecting pathology such as demyelination and axonal loss. Cardiovascular risk factors (CVR)—including systolic blood pressure (SBP), heart rate, and cholesterol—are linked to WMH burden. This study examines how longitudinal CVR influences WMH volume and microstructure using quantitative MRI (qMRI).

**Methods:** We analyzed data from 153 participants (86 women) in the BrainLaus study, a sub-cohort of CoLaus|PsycoLaus (Lausanne, Switzerland), each with at least three CVR assessments over an average of 14.45 years. CVR metrics included SBP, DBP, BMI, bioimpedance, WHR, heart rate, glucose, insulin, and lipid profiles. MRI was performed on a 3T Siemens Prisma using FLAIR, T1, multi-echo FLASH, and DWI sequences. WMHs were segmented with a ResUNet-based algorithm. Quantitative maps (MTsat, R1, R2\*) were generated. CVR trajectories were modeled using splines, and area under the curve (AUC) was computed and normalized per participant. Statistical analyses included FDR-corrected linear models with sex interactions.

**Results:** Higher CVR (e.g., SBP, LDL, WHR, glucose) was associated with increased WMH volumes, with stronger effects in women for SBP, LDL, total cholesterol, and triglycerides. qMRI revealed sex-specific microstructural changes: in women, lipid-related CVR correlated with increased extracellular water (MD, ISOVF); in men, hypertension and heart rate were linked to lower myelin content (MT, R1) and increased g-ratio, indicating myelin thinning.

**Discussion:** CVR impacts WMH differently in men and women, suggesting distinct underlying mechanisms. These findings support sex-specific strategies for managing CVR to preserve white matter health and reduce cognitive decline risk.

## **P41-B: Mitochondrial Transfer between Astrocytic and Neuronal Cells Is Impacted By Abnormal Tau Protein**

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Tauopathies are a group of neurodegenerative diseases characterized by the pathological accumulation of abnormal tau protein. A consequence of tau pathologies is mitochondrial dysfunctions, which affect essential processes such as mitochondrial transport, bioenergetic, and dynamic. Given the high energy demands of neurons, tau-induced mitochondrial impairment significantly contributes to neuronal vulnerability and degeneration. Studies have revealed that cells can transfer mitochondria between them to help energy-deficient cells. This process, known as intercellular mitochondrial transfer, can occur via two different pathways: an indirect transfer via extracellular vesicles and a direct transfer via tunneling nanotubes and gap junctions. Considering the impact of pathological tau on mitochondrial transport and cytoskeletal dynamics, we hypothesized that abnormal tau protein negatively affects intercellular mitochondrial transfer. In this study, we investigated intercellular mitochondrial transfer between astrocytic and neuronal cells under tauopathy conditions. Using A172 astrocytic cells and SH-SY5Y neuronal cells bearing or not the P301L tau mutation, we observed that abnormal tau surprisingly enhances mitochondrial transfer from astrocytic to neuronal cells, predominantly through contact-dependent mechanisms. While the fate of transferred mitochondria was essentially unchanged, a trend toward impaired mitophagy was observed in neuronal cells bearing the P301L mutation. To summarise, our data highlight a novel pathway by which abnormal tau protein impacts mitochondrial function, namely the transfer of astrocytic mitochondria to neuronal cells

## **P42-B: Molecular, genetic and functional screening to identify modifiers of Neurodegenerative diseases**

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Cognitive decline occurs naturally with aging but is more pronounced in proteinopathies such as Alzheimer's disease and frontotemporal dementia. Key pathological proteins, including TDP-43 and Amyloid- $\beta$ , drive many of the molecular and behavioral changes observed in these disorders. Using the powerful genetic tools of *Drosophila melanogaster*, we investigate these mechanisms in a spatio-temporal manner.

By expressing human TDP-43 and Amyloid- $\beta$  in the neurons of flies, we recapitulate memory impairments as seen in patients. Behavioral testing at different time points allows us to track disease progression over time. Through immunostaining, we examine the localization and aggregation dynamics of these proteins and of their fly homologues, revealing age-dependent alterations.

To connect molecular signatures with behavior, we perform single-cell transcriptomic profiling of fly brains expressing the aforementioned proteins and compare these data to human datasets, identifying conserved gene expression changes. This cross-species approach enables us to pinpoint potential therapeutic targets, which we rapidly test in our model system. We evaluate known memory modulators, repurposed drugs such as anti-tumor compounds, and novel molecular pathways to identify modifiers that can alleviate disease phenotypes. Together, this work establishes a robust and versatile pre-clinical platform for dissecting neurodegenerative mechanisms.

### **P43-B: Perivascular spaces in memory center patients with dementia with Lewy bodies and Alzheimer's disease**

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**Introduction:** Enlarged perivascular spaces (ePVS) are one of the imaging features of cerebral small vessel disease, a common co-pathology in patients with dementia with Lewy bodies (DLB) and Alzheimer's disease (AD). Moreover, they are part of the brain glymphatic system. In this study we characterized ePVS in DLB and AD cohorts referred to a memory center.

**Methods:** In this retrospective study, we collected data from patients with a clinical DLB diagnosis or clinico-biological AD diagnosis, evaluated at our memory center (Leenaards Memory Center, Lausanne University Hospital, Switzerland). Patients were assessed for ePVS at the level of the basal ganglia (BG) or centrum semiovale (CSO), using established guidelines and scores. Differences in prevalence between the two groups were investigated. Regression model was used to evaluate the association between ePVS cognition as expressed by Montreal Cognitive Assessment (MoCA) test.

**Results:** We included 71 DLB and 71 age- and gender-matched AD patients. Both patients with DLB and AD presented with a high ePVS score at the level of the CSO (median (interquartile range)= 3.0 (1.0) on a score ranging from 0 to 4). At the BG level, DLB patients presented with a median score of 2.0 (1.75), while AD patients presented with a median score of 1.0 (1.0). When compared, DLB patients had higher ePVS load in the BG ( $p = .011$ ) and CSO ( $p = .004$ ). No association was found between ePVS and MoCA.

**Discussion:** DLB and AD patients present with a high load of CSO ePVS. At both CSO and BG level, DLB patients present with a greater ePVS load compared to AD, possibly related to glymphatic system dysfunction. EPVS do not seem to impact on cognition on these patients.

## **P44-B: Protein fingerprints of brain-derived extracellular vesicles predict types of tau pathology**

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Tauopathies are neurodegenerative disorders characterized by the abnormal intracellular aggregation of different tau protein isoforms. To date, there is limited understanding and few elements to distinguish the cellular consequences associated with the accumulation of tau 3R and 4R isoforms. To further our understanding of the underlying mechanisms behind these specific disruptions in tau homeostasis, we investigated the content of extracellular vesicles present in the brain parenchyma of patients diagnosed with 3R and 4R tauopathies, and compared these profiles to those of healthy controls.

## **P45-B: Restoring the Neurogenic Niche: Astrocytic Modulation of Microglial Reactivity in Alzheimer's Disease**

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Alzheimer's disease (AD) is a progressive neurodegenerative disorder marked by cognitive decline, memory loss, and behavioral changes. A key pathological feature of AD is the disruption of adult hippocampal neurogenesis (AHN), a process essential for learning, memory, and emotional regulation. The neurogenic niche, where AHN occurs, is tightly regulated by glial cells—particularly microglia and astrocytes.

Microglia influence neurogenesis through immune surveillance and cytokine secretion, while astrocytes support neuronal development and synaptic integration. Although both cell types are essential for maintaining niche homeostasis, their interactions in the context of AD remain poorly understood.

Our research aims to elucidate the glial crosstalk within the neurogenic niche and explore therapeutic strategies to restore its function in AD. Previous findings from our lab demonstrated that astrocyte-secreted molecules attenuate microglial activation, reduce pro-inflammatory cytokine release, and enhance neurogenesis.

In the APP/PS1 mouse model of AD, we observed early impairments in AHN, with a more pronounced and earlier onset in females (4 months) compared to males (6 months). This was characterized by a decrease in doublecortin-positive (DCX+) immature neurons, despite increased proliferation. Building on this, we compared the effect of astrocyte-derived molecules and Toll-like receptor inhibition on APP/PS1 mice, on the neurogenic niche, adult neurogenesis and cognitive function.

Our preliminary data suggest that targeting astrocyte-microglia interactions can rebalance the neurogenic niche, promote neurogenesis, and potentially alleviate cognitive deficits in AD. This study highlights the therapeutic potential of modulating glial communication to combat neurodegenerative diseases.

## P46-B: Sortilin 1 modulates ApoE levels and tau seeding in an astrocytic model

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Members of the VPS10-domain receptor family (SORT1, SORL1, SORCS1, SORCS2, SORCS3) are key regulators of vesicular trafficking and protein sorting, and all five genes have been genetically associated with Alzheimer's disease (AD). Among them, SORL1 displays hybrid features of the LDL receptor and VPS10 families and has been implicated in amyloid- $\beta$  (A $\beta$ ) trafficking and clearance. We recently demonstrated that SORL1 also promotes tau internalization and seeding, suggesting that VPS10-domain receptors could represent a broader mechanistic link between lipid metabolism and tau propagation.

Building on this finding, we investigated whether SORT1 (sortilin), another VPS10-domain family member, contributes to tau trafficking in astrocytes. In hepatocytes, sortilin regulates VLDL trafficking and secretion, and its activity is modulated by the metabolic state. To test whether similar principles apply to astrocytes, we treated CCF-STTG1 cells with small-molecule sortilin modulators (AF38469 and Cpd984) under starved or fed conditions and quantified both intracellular and secreted ApoE. Sortilin modulation produced distinct effects on ApoE secretion depending on the metabolic state. Furthermore, using an astrocytic tau biosensor cell line, we found that pharmacological inhibition of sortilin significantly reduced tau seeding activity.

Together, these findings identify sortilin as a metabolism-sensitive regulator of ApoE secretion and tau propagation in astrocytes. They support the broader concept that molecular pathways governing lipoprotein handling in glial cells may directly influence the intercellular spread of tau pathology in AD.

## **P47-B: Stopping Parkinson's disease at early stages**

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In Parkinson's disease a protein called alpha-Synuclein (aSyn) self-aggregates to form protein clumps which are toxic for the cells of the brain. Although aSyn aggregates are invariably found in the brain of people suffering PD, it has been long reported that they appear first in the peripheral nervous system such as the olfactory bulb and enteric neurons, and only after several years of disease progression they reach certain areas of the brain. During this long period, PD is asymptomatic opening opportunities for therapeutic applications aimed to stop the disease at these early stages. For this reason, in our laboratory we are making huge efforts to understand not only the 3D structure of the aggregates but also the mechanisms used by aSyn self-associates and travel from the periphery to the (mid)brain through different neuroanatomical structures.

In our recently published works, we have shown that aggregated aSyn can be transmitted from one cell to another via sequential steps of secretion and internalization. In this process, the aggregates are released from one cell to the extracellular space, and is subsequently taken up by a neighbor cell. Once inside the new recipient cell, the aggregates recruit the functional aSyn from the recipient cell to create more aggregates. This "infective" mechanism not only perpetuates the vicious cycle of aggregate formation and amplification, but also allows aSyn aggregates to travel longer distances reaching, after 5 to 10 years, the cells of the brain that are crucial for PD symptomatology.

In our poster we will show advances on novel therapeutic approaches to stop PD at early stages. They include the generation of a mouse model of aSyn aggregate transmission and PD progression, as well as the identification of cellular mechanisms and therapeutic targets that can be used to stop these two processes.

## **P48-B: Structure-function relationship of alpha-synuclein fibrils derived from distinct synucleinopathies**

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The aggregation of the protein alpha-synuclein ( $\alpha$ Syn) is a hallmark of several neurodegenerative diseases, including Parkinson's disease (PD), Dementia with Lewy bodies (DLB), and Multiple System Atrophy (MSA). Here, we aim to characterize the structure-function relationship of disease-specific  $\alpha$ Syn fibrils at a proteome-wide level with a novel structural proteomics method.

We employ the Limited proteolysis coupled with mass spectrometry (LiP-MS) to detect structural changes and altered protein-protein interactions across thousands of proteins, with a resolution of ~10-20 amino acids. This enables LiP-MS to provide structural insights that remain inaccessible to other omics approaches.

In vitro, in neurons and directly in native patient brain homogenates, we show that pathogenic  $\alpha$ Syn from distinct synucleinopathies (PD, DLB and MSA) exhibit structural differences. Furthermore, we found that fibrillar structural differences are associated with distinct structural responses in neuronal proteomes and pathways. Selected hits were validated using CRISPR-based tools. Our findings reveal that fibrillar structural differences directly influence fibril interactomes and neuronal responses.

## P49-B: Testing the Amyloid Cascade in Alzheimer's Disease: Insights from AA-2024 Biological-Clinical Criteria

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### Background and Objectives:

The amyloid cascade hypothesis suggests Alzheimer's disease (AD) progresses from amyloid deposition to tau pathology, neurodegeneration, and cognitive impairment. The 2024 Alzheimer's Association (AA-2024) criteria introduce a two-dimensional biological-clinical staging system to account for copathologies and resilience. We estimated the proportion of individuals whose trajectories align with the amyloid cascade.

### Methods:

Cross-sectional data from 256 amyloid-positive participants (mean age 72.7 years; 51% female) in the Alzheimer's Disease Neuroimaging Initiative (ADNI) were classified in a 4×4 biological/clinical matrix. Biological stages (A to D) were based on amyloid and tau PET imaging, using five cutoff methods from Jack et al. (2017). Clinical stages ranged from cognitively unimpaired to dementia. Participants were categorized as (1) compliant (aligned biological and clinical stages), (2) resilient (advanced biological stage, milder clinical symptoms), or (3) copathologic (early biological stage, advanced clinical symptoms). Observed distributions were compared with hypothetical zero- and high-penetrance scenarios using  $\chi^2$  tests.

### Results:

Between 31%–36% of individuals were compliant with the amyloid cascade, depending on the tau-PET cutoff. Compliance rates were higher than in a zero-penetrance model but lower than in a high-penetrance model ( $p < 0.01$ ). Copathologic and resilient patterns varied significantly (17%–63% and 6%–52%, respectively;  $p < 0.001$ ).

### Conclusion:

Only about one-third of amyloid-positive individuals exhibited strict compliance with the amyloid cascade sequence. These findings emphasize the considerable influence of resilience and copathologies in modulating disease progression beyond the traditional amyloid-first model.

## P50-B: Tract-Specific Microstructural Vulnerability Linked to Vascular Risk and White Matter Hyperintensities

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White matter hyperintensities (WMH), common in ageing, are linked to small vessel disease. Neuropathology indicates heterogeneity within WMH and damage extending into normal-appearing white matter (NAWM). These diffuse changes may reflect distinct vascular and neurodegenerative mechanisms that vary across white matter (WM) regions. We used quantitative MRI (qMRI) and multi-shell diffusion-weighted imaging (DWI) to detect NAWM microstructural changes associated with WMH burden and cardiovascular risk factors (CVRF), and to assess whether these changes vary across tracts.

We analyzed 165 participants (mean age = 73.9±6.7 years, 94 females) from the BrainLaus epidemiological cohort. qMRI and DWI provided metrics sensitive to myelin/iron (MTsat, R1, R2\*), axonal density/organization (FA, ICVF, OD), and oedema (MD, ISOVF). WMH were segmented from FLAIR using WHITE-Net deep-learning algorithm. WM tracts (n=27) were defined with TractSeg. Associations were tested with linear regression for global analyses and linear mixed-effects models for tract-level analyses (FDR-corrected). CVRF burden was quantified using SCORE2.

Higher WMH volume was associated with widespread NAWM alterations, including lower MTsat, R1, R2\*, FA, and ICVF, and higher MD (absolute  $\beta$  range 0.22-0.41;  $p < 0.001$ ), consistent with demyelination, axonal loss, and oedema. These associations differed across tracts (tract  $\times$  WMH interaction:  $p < 0.05$  for all metrics except MTsat), with strongest effects in the anterior corpus callosum, thalamic-premotor, and superior longitudinal fasciculus. CVRF burden was also linked to impaired NAWM microstructure across all metrics except OD (absolute  $\beta$  range 0.17-0.41;  $p < 0.001$ ). After adjusting for WMH volume, only MTsat, R1 (myelin-sensitive metrics), and ISOVF remained significant.

qMRI and DWI capture NAWM microstructural changes associated with WMH and CVRF in vivo. Vascular risk may trigger early myelin damage, while axonal degeneration emerges with WMH lesions, reflecting later or secondary processes. Tract-level variation highlights spatial heterogeneity in white matter susceptibility.

## **P51-B: Two-photon calcium imaging reveals increased local propagating calcium waves in cerebral organoids with APP mutation**

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Cerebral organoids are widely used to model aspects of human brain development, function and disease. However, little is known about the longitudinal neuronal network dynamics present in organoids, or how these dynamics are affected in Alzheimer's disease (AD). Here, we aimed to characterise these dynamics during the development of organoids, by recording neuronal activity at the single-cell level using two-photon Ca<sup>2+</sup> imaging.

We cultured iPSC-derived organoids from a control line (KOLF2.1J) and an isogenic AD line harbouring a homozygous amyloid precursor protein (APP)V717I mutation. We then undertook two-photon Ca<sup>2+</sup> imaging throughout the spherical organoid structure, labelled with the indicator Cal520-AM, between Days 80-300.

We identified three distinct modes of spontaneous activity in both organoid lines: unsynchronous activity, synchronous activity and local propagating Ca<sup>2+</sup> waves. The waves were a surprising network dynamic that appeared from Days ~100-120 onwards, which consisted of a propagating radius of Ca<sup>2+</sup> transient events across multiple cells, initiating from a central cell before propagating to adjacent neurons. Pharmacological experiments revealed the waves are not primarily initiated in individual neurons by action potentials but, rather, as a result of spontaneous Ca<sup>2+</sup> release from internal stores, and propagate to surrounding neurons via synaptic connections.

In the APP mutant line, we observed waves to appear earlier in development, Day ~100 compared to Day ~120 in control, and significantly more spontaneous waves compared to controls, suggesting the APP mutation may have an impact on this network activity in human cells.

In summary, by employing two-photon Ca<sup>2+</sup> imaging, we reveal that organoids develop functionally interconnected networks of neurons which display multiple types of spontaneous activity, including local propagating Ca<sup>2+</sup> waves. To the best of our knowledge, these waves have not been described previously and may be significant in the early development of human neuronal networks, and significantly affected by an APP mutation.

## Category: Genetics

### **P52-C: Biological characterization of Frontotemporal Dementia (FTD) using human induced Pluripotent Stem Cells (hiPSCs): an innovative approach of the Swiss FTD network**

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Human induced pluripotent stem cells (hiPSCs) hold a great potential for treating neurodegenerative diseases, such as frontotemporal dementia (FTD) – the second cause of neurodegenerative dementia in individuals younger than 60 - due to their ability to differentiate into various cell types found in the central nervous system. By generating patient-specific hiPSCs and directing their differentiation into neuronal populations, personalized disease models can be created, offering unique opportunities for drug screening, disease mechanism understanding, and potential cell-based therapies.

After an initial single case study where we thoughtfully described a novel missense progranulin (*GRN*) mutation in a behavioral variant FTD (bvFTD) with biological hallmarks of TDP43-FTD with an hiPSC model, we introduced this technique with various selected FTD patients in Lausanne, with phenotypes ranging from progressive supranuclear palsy (PSP) to semantic dementia (SD).

Having established this technique by bringing together the clinical data of the Leenaards Memory Center in Lausanne University Hospital and the innovative development of the iPSC platform in the Center for Psychiatric Neuroscience (CPN) in Lausanne University Hospital, we aim at implementing it at a national level bringing together the clinical expertise of members of the Swiss-FTD network to our local knowledge.

### **P53-C: Cognitive rejuvenation through partial reprogramming of engram cells**

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Counteracting cognitive decline is an important goal in regenerative medicine. Recently, partial cellular reprogramming has emerged as a promising strategy to restore cellular function and promote tissue regeneration, but whether this approach can be targeted to sparse cell types responsible for cognitive frailty is not known. In aged mice and mouse models of Alzheimer's Disease (AD) engram cells responsible for memory formation are functionally impaired, but the underlying molecular mechanisms of this impairment and potential means to rescue it have not been explored. We found that partial reprogramming of engram cells in aged mice and models of AD by OSK-mediated gene therapy restored engram reactivation, reversed the expression of age and disease-related cellular markers and re-established aberrant epigenetic and transcriptional alterations related to synaptic plasticity. Importantly, irrespective of the brain area targeted or the behavioural paradigm employed, it also recovered learning and memory capacities towards those observed in healthy young animals, suggesting cognitive rejuvenation. These results posit that partial reprogramming targeted to sparse cell populations in the brain can be exploited to restore cognition during aging and disease.

## **P54-C: Investigation of genome engineered humanized ALS/FTD Drosophila models**

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Amyotrophic Lateral Sclerosis (ALS) and Frontotemporal Dementia (FTD) represent the two endpoints of a single neurodegenerative disease continuum. Increasing evidence suggests that RNA-binding proteins, such as TDP-43 and FUS, play a critical role in the pathogenesis of these diseases.

It has been hypothesized that TDP-43 and FUS loss-of-function (LoF) or gain-of-function (GoF) mechanisms could contribute to ALS/FTD pathogenesis, however most animal models only address some of these aspects without fully recapitulating the heterogeneity and progression of the disease.

We used CRISPR/Cas9 technology to generate humanized ALS/FTD Drosophila models, in which the Drosophila ortholog of TDP-43 and FUS is replaced with the human TDP-43 or FUS sequence, to investigate how patient-derived mutations in these genes induce ALS/FTD symptoms and disease progression, without bias towards LoF or GoF mechanisms.

We found that gene replacement with human TDP-43 or FUS wildtype (WT) fully rescued the lethality defects of the corresponding Drosophila null mutants, which display normal motor behavior, lifespan and NMJ morphology. These results confirmed that the functions of TDP-43 and FUS are highly conserved across species, making Drosophila a powerful system for in vivo investigation of FTD-linked mutations. Unlike Drosophila expressing the WT sequence of the genes, animals that expressed human TDP-43 or FUS with disease-associated mutations exhibited reduced lifespan as well as impaired motor ability. In agreement with observations made in some of the FTD rodent models, mutant humanized Drosophila also exhibited evening time motor hyperactivity but appeared to be less active during other times of the day. Currently, we are investigating defects in central motor circuits that may underlie the locomotion hyperactivity observed in these humanized FTD models as well as performing RNA-sequencing to identify disease-modifying targets, which could provide the basis for new ALS/FTD therapeutics.

## **P55-C: Pathogenicity of a missense GRN variant in Frontotemporal Dementia**

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Mutations in the progranulin (GRN) gene are a major cause of Frontotemporal Lobar Degeneration (FTLD). To date, over 65 variants have been identified, mostly nonsense or splice-site mutations, resulting in a loss of function with progranulin (PGRN) haploinsufficiency and TDP-43 neuropathology. However, it has currently been not proven that missense mutations may also cause FTLD.

Here, having diagnosed a patient with FTLD presenting borderline levels of PGRN and a novel missense GRN mutation, we aim to assess the pathogenicity of this novel variant using human induced pluripotent stem cells (hiPSCs) as a model.

For this study, we reprogrammed hiPSCs from the aforementioned patient's cells. Then, we generated and phenotyped neurons and microglia derived from these hiPSCs. Last, using CRISPR-Cas9 technology, we are correcting the GRN missense mutation in the patient-derived hiPSCs and introducing the mutation in control hiPSCs to firmly demonstrate its pathogenicity.

Characterization of patient-derived neurons revealed several hallmarks of GRN-FTLD (cytoplasmic TDP-43, lysosomal dysregulation, and cell death). We are now characterizing patient-derived microglia and their role in neuroinflammation and neurotoxicity. These experiments demonstrate a disease-associated phenotype in hiPSC-derived brain cells from this patient. Last, characterization of CRISPR-edited cells will allow us to definitely uncover whether this missense mutation is the cause of the patient's pathology.

Our model provides for the first time biological insights into the pathogenic role of missense GRN mutations and offers a model to test potential treatments on patient-derived neurons and microglia.

## Category: Therapy and intervention

### **P56-D: Anti-amyloid drugs for patients with idiopathic Normal Pressure Hydrocephalus and positive Alzheimer's disease biomarkers?**

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**Introduction:** Anti-amyloid monoclonal antibodies have been recently approved for Alzheimer's disease (AD). Idiopathic normal pressure hydrocephalus (iNPH) is often associated with AD. Although the presence of any degenerative comorbidity constitutes an exclusion criterion for anti-amyloid therapy, the frequent co-occurrence of these two conditions, coupled with the potential reversibility of iNPH, may warrant a dedicated assessment

**Objectives:** We aimed to identify the prevalence and characteristics of iNPH patients with AD-positive biomarkers potentially eligible for anti-amyloid treatments.

**Methods:** We retrospectively identified iNPH patients according to international criteria. Demographic, clinical, CSF and MRI data were collected. AD positive status was defined as A+T+ and exclusion criteria for anti-amyloid drugs were evaluated.

**Results:** Among 81 iNPH patients (78.9 y.o (±5.1)) referred from Neurosurgery Service to Leenaards Memory Center of the Lausanne University Hospital (Switzerland) from May 2019 to December 2023, 11 (13.6%) of iNPH patients presented AD positive biomarkers and 7 (8.6%) were eligible for anti-amyloid drugs. Among ineligible patients, 2 (18%) had more than 4 microbleeds at brain MRI, 1 (9%) for CDR>1 and 1 (9%) had active anticoagulant treatment. Clinical and radiological features were similar between iNPH patients eligible or ineligible to treatment.

**Discussion:** Among iNPH patients with AD comorbidity, the majority could be eligible to AAT according to Clarity AD inclusion criteria. Apart from iNPH radiologic signs, the main exclusion criteria were based on imaging findings, as in previous studies; we found similar percentage (around 9%) of patients excluded due to dementia severity and/or anticoagulant treatment. Our study did not find any clinical or radiological features that correlate with the presence of AD biomarkers in iNPH.

**Conclusions:** While only a minority of iNPH patients qualify for anti-amyloid drugs, it is essential to develop a clinical strategy to stratify the therapeutical approaches for these patients.

## P57-D: Blarcamesine: A New Oral Treatment Approach for Alzheimer's Disease

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The ANAVEX2-73-AD-004 phase IIb/III trial was a randomized, double-blind, placebo-controlled study lasting 48 weeks. It evaluated the efficacy and safety of blarcamesine, an oral sigma-1 receptor agonist aimed at restoring autophagy, in patients with early-stage Alzheimer's disease (AD).

A total of 508 patients were randomized to receive either blarcamesine (30 mg or 50 mg; n = 338) or placebo (n = 170) once daily by mouth.

The primary endpoints were changes in ADAS-Cog13 and ADCS-ADL scores. Secondary endpoints included CDR-SB score and biomarkers such as the plasma A $\beta$ 42/40 ratio and brain volume measured by MRI. Analyses were conducted using mixed models for repeated measures, Welch's t-test, and general linear models.

Among the 462 participants in the intent-to-treat (ITT) population (average age: 73.7 years; 48.7% women), 73.1% completed the trial. The blarcamesine group showed statistically significant improvements on the ADAS-Cog13 (-2.027; P = 0.008) and CDR-SB (-0.483; P = 0.010). The ADCS-ADL showed a positive trend, though it was not statistically significant. Treatment positively impacted the plasma A $\beta$ 42/40 ratio and reduced brain atrophy. A genetic analysis revealed an even greater benefit (49.8%) in patients with the wild-type SIGMAR1 gene. The safety profile was favorable.

Blarcamesine may represent a promising new oral therapeutic option for early-stage AD, either as a complement to or an alternative to current anti-amyloid treatments.

## **P58-D: Brain mechanisms underlying closed-loop auditory stimulation during slow-wave sleep in a neurodegeneration model**

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The deepest stage of non-rapid eye movement (NREM) sleep, slow-wave sleep (SWS), is essential for brain and body health, maintaining homeostasis, and supporting cognition, brain clearance, and overall restoration. Parkinson's disease (PD) and other neurodegenerative disorders involve dysregulation of pathways that modulate the sleep-wake cycle, leading to early prodromal symptoms that may accelerate or worsen disease progression. In mice, closed-loop auditory stimulation (mCLAS) targeting slow waves during sleep has been shown to deepen SWS and alleviate PD-specific sleep-wake disturbances, perhaps slowing disease progression. However, the underlying neural mechanisms by which mCLAS exerts its beneficial effects remain unclear. The corticothalamic pathway connects cortical and thalamic regions, including the thalamic reticular nucleus (TRN), ventral posteromedial nucleus (VPM), and auditory cortices. Moreover, this pathway is crucial for generating and modulating delta waves and sleep spindles, hallmarks of healthy sleep, as well as for regulating the flow of somatosensory information. Could therefore mCLAS act on macrostructural sleep-wake improvement via regulation of corticothalamic activity in PD? To address this knowledge gap, we will investigate how mCLAS modulates corticothalamic circuits' activity in a mouse model of PD (A53T-M83). We will combine *in vivo* multi-unit activity and local field potential recordings with mCLAS and, complementarily, perform *ex vivo* whole-brain mapping of immediate-early gene expression using tissue clearing and 3D imaging to determine cellular activation patterns. Our findings will start to elucidate how mCLAS influences corticothalamic connectivity and guide the refinement of oscillotherapy-based neurotechnologies for neurodegeneration patients.

## P59-D: Computational engineering of Bax-inhibiting peptides

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The proteins of the Bcl-2 family play crucial roles in regulating apoptosis. It is divided into pro-survival and pro-apoptotic proteins that determine cellular fate. In particular, Bax is a crucial executor of apoptosis as its activation initiates the apoptotic phenotype. Hence, targeting this protein represents an attractive therapeutic approach, which can aid in regulating apoptotic signalling and potentially contribute to the development of novel therapies against cancer and neurodegenerative diseases.

Here, we introduce a digital paradigm, which relies on rational design and computer simulations to develop and validate peptide-based agents that bind to Bax, thereby inhibiting its apoptotic properties. The peptides are rationally designed and optimized to bind to Bax starting from the crystal structures of affimers in a complex with Bcl-2 proteins. Next, molecular dynamics (MD) simulations are employed to probe the stability of the Bax-peptide complexes and to estimate the binding free energies. The results show that the designed peptides bind with high affinity to Bax. Two of the designed peptides bind in the canonical hydrophobic groove (BH1 domain) of Bax and one peptide binds to the outside of the BH3 domain ( $\alpha$ 2-helix). Notably, the peptides restrict the flexibility of the  $\alpha$ 1- $\alpha$ 2 loop, modulating the trigger bottom site associated with toxicity.

All in all, the results highlight the potential of these peptides as valuable tools for further exploration in modulating apoptotic pathways and set the structural foundation for a machine learning powered engine for peptide design.

## **P60-D: Exploring closed-loop auditory stimulation's role in retinal glymphatic clearance in Alzheimer's Disease model mice**

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Alzheimer's disease (AD) is characterized by progressive accumulation of amyloid- $\beta$  (A $\beta$ ) and neuronal loss, with pathological changes emerging in both brain and retina years before clinical symptoms develop. Early detection of retinal thinning and A $\beta$  deposition in AD patients may provide a noninvasive biomarker for prodromal diagnosis. The glymphatic system (GS) has been shown to facilitate the clearance of metabolic waste both in brain and retina, including A $\beta$ , and is most active during slow-wave sleep. Therefore, enhancing slow-wave activity (i.e. sleep depth) may represent a promising therapeutic approach to promoting protein clearance. Our preliminary data demonstrated a significant reduction in retinal amyloid precursor protein (APP) load in an AD mouse model following 10 days of closed-loop auditory stimulation (CLAS), a technique that boosts slow-wave activity through phase-targeted auditory stimulation. This project will further investigate whether CLAS can reduce retinal A $\beta$  load and preserve retinal integrity. We will assess the structural and molecular correlates of CLAS treatment, including retinal thickness (optical coherence tomography, OCT), A $\beta$  load, and aquaporin-4 (AQP4) expression and recruitment to perivascular sites. In addition, we will examine functional parameters such as retinal ganglion cell activity (multielectrode array, MEA), intraocular pressure, and circadian rhythms, all of which are regarded as potential mechanistic pathways linking sleep enhancement to GS-mediated clearance. By establishing causal links between CLAS-enhanced sleep, retinal GS function, and AD pathology, this research aims to validate the retina as both a therapeutic target and monitoring tool for sleep-based interventions for AD patients. The potential of combining CLAS with retinal biomarkers as a non-invasive strategy for the early detection and modification of AD progression will also be explored.

**P61-D: Mechanistic insights of coordination cage-mediated siRNA-delivery in Alzheimer's disease. A multidisciplinary approach from synthesis and simulations to in vivo validation**

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Neurodegenerative disorders, like Alzheimer's disease (AD), are projected to surpass cancer as the leading cause of death in the coming decade. Because of the complex neuropathology of AD and the protective blood-brain barrier, drug development is challenging. Gene therapeutics, such as small interfering RNA (siRNA), offer the possibility to target the underlying cause of the disease, potentially enabling more effective treatments and even a cure. Traditional therapies, using viral vectors, face issues with administration, stability and customization. Non-viral nanocarriers address these challenges due to their smaller size, high bioavailability and modularity, making them a promising solution for selective brain targeting. In particular, metal organic cages (MOCs) have shown potential as novel nanocarriers for cell-specific delivery of siRNA in cancer cells. [1]

In this study, we rationally design and synthesize metal organic cages as potent brain targeting nanocarriers. We combine molecular dynamics simulations and spectroscopy to investigate the interactions between the nanocage, siRNA and the neuronal membrane, and to assess the binding and stability of the nanocage-siRNA complex. Additionally, we evaluate their functional potential in a preclinical Alzheimer's disease mouse model. Gaining insights through computational, spectroscopic and in vivo studies, the functionalization of the nanocarrier is further optimized to enhance efficacy, targeting and toxicity.

The results show that the nanocages bind to siRNA with high affinity and are able to deliver their genetic cargo into AD mouse hippocampus, where siRNA is successfully internalized and retains its silencing ability. These findings pave the way for optimizing and diversifying the current strategy and help to advance the development of treatments for brain-related diseases.

[1] Bobylev, E. O., Zeng, Y., Weijertse, K., Koelman, E., Meijer, E. M., de Bruin, B., Kros, A., Reek, J. N. H. The application of M12L24 nanocages as cell-specific siRNA delivery agents in vitro. *Chem* 2023, 9, 1578–1593.

## P62-D: Metformin and Its Analogues in Autophagic Degradation of $\alpha$ -Synuclein Condensates

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Parkinson disease (PD) is one of the most prevalent neurodegenerative diseases, characterized by the abnormal alpha-synuclein ( $\alpha$ -syn) aggregation. While amyloid protein cascade hypothesis remains a main explanation for PD pathology, no chemical drugs targeting  $\alpha$ -syn oligomers are success in clinic, largely due to their transient and heterogeneous nature. Recent studies have identified a distinct intermediate state in  $\alpha$ -syn aggregation: liquid-like condensates at nanoscale known as nanoclusters, which are more dynamic and less cytotoxic than traditional oligomers. In this study, we demonstrate that metformin and its analogues can form larger  $\alpha$ -syn nanoclusters, then more easily directing their fate toward autophagic degradation rather than fibril formation. Interestingly, we also show that in the presence of metformin,  $\alpha$ -syn could rescue the role of LC3 in stabilizing membranes during autophagosome formation. These findings offer novel insight into the aggregation landscape of  $\alpha$ -syn, suggesting that nanoclusters represent a promising therapeutic target. Moreover, our results highlight the potential of biguanide-based compounds as dual-function agents—modulating  $\alpha$ -syn phase behavior while enhancing its clearance via autophagy—for future PD treatment strategies.

## P63-D: Microbial Modulation of the Gut–Brain Axis in Alzheimer’s Disease

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Alzheimer’s disease (AD) is the leading cause of dementia, affecting 55.2 million people globally. The highest regional burdens were reported in the Western Pacific and Europe, according to the World Health Organization, 2019. AD is characterized by cognitive decline hallmark neuropathological features, including amyloid-beta plaques and phosphorylated tau tangles (pTau), and genetic risk factors such as carrying the Apolipoprotein E (APOE)  $\epsilon$ 4 allele. Recent studies have uncovered pathophysiological links between the gut microbiome and brain amyloidosis, particularly via bacterial lipopolysaccharides and short-chain fatty acids, highlighting the relevance of gut microbiota in AD pathology.

In this study, we investigate associations between gut microbiota composition and key Alzheimer’s disease features—amyloid, pTau, and APOE genotype—alongside clinical assessments of cognitive status. Comprehensive microbial profiles were generated from stool-derived DNA using advanced shotgun metagenomic sequencing from 551 participants at the Memory Center of Geneva University Hospital. The cohort included individuals spanning the cognitive spectrum, from unimpaired to cognitively impaired.

Microbial abundance and prevalence profiles were obtained using read-based taxonomic profilers mOTUs and Sylph. These profiles were incorporated into a Bayesian probabilistic modelling to examine associations with AD pathology and related clinical indicators. This study hypothesizes that bacterial taxa significantly reduced in (1) cognitively impaired individuals, (2) those with amyloid and pTau positivity, and (3) carriers of the APOE  $\epsilon$ 4 allele (e.g.,  $\epsilon$ 2/ $\epsilon$ 3 vs  $\epsilon$ 3/ $\epsilon$ 4 genotypes) may serve as promising candidates for targeted probiotic interventions.

Our findings revealed several species within the genera *Dysosmobacter*, *Blautia*, *Bacteroidetes*, *Lawsonibacter*, and *Faecalibacterium* emerging as top candidates. Results also suggest the presence of potentially novel species within these genera, warranting further phylogenomic analysis to resolve species- and strain-level diversity. Future pan-genome analyses will aim to elucidate the metabolic potential of these probiotic candidates. Altogether, this study lays the groundwork for microbiome-based interventions in Alzheimer’s disease, advancing the path toward precision probiotic treatment.

**P64-D: Overexpression of UCP4 in astrocytes induces fatty acid oxidation for mitochondria respiration fuelling**

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A growing body of evidence recognizes astrocytes' ability to oxidize fatty acids as an energy substrate, a process that appears critical for higher-order cerebral functions. However, the signals that reprogram astrocytes from primarily glycolytic metabolism to fatty acid utilization remain unclear. Here, we provide the first evidence that increased expression of mitochondrial uncoupling protein 4 (UCP4) in primary astrocytes induces a metabolic shift favoring  $\beta$ -oxidation. UCP4 overexpression upregulate genes associated with fatty acid uptake, synthesis, transport, and metabolism, enabling fatty acids to fuel mitochondrial respiration while redirecting glucose-derived pyruvate toward lactate production. This astrocytic metabolic shift prevented neurodegeneration in the familial Alzheimer's disease mouse model 5xFAD. Mice treated with an adeno-associated virus (AAV) overexpressing UCP4 did not develop memory impairments at 6 months of age. Moreover, brain levels of A $\beta$ 1-42 as well as synaptic markers such as PSD95 were rescued. Our data suggest that inducing a metabolic shift toward  $\beta$ -oxidation could provide a biological framework for developing treatments for neurodegenerative diseases such as AD.

## **P65-D: Recruitment, enrollment and retention strategies in Clinicals Trials: The Geneva Memory Center experience**

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With the growing number of people diagnosed with Alzheimer's disease (AD), it has become a major public health issue. In this context, clinical trials are essential to develop effective treatments and improve patient care. As part of translational medicine, memory clinics play a key role in facilitating access to innovative therapies. The Geneva Memory Center (GMC) follows this model by integrating research into its clinical practice. Over the past seven years, GMC has participated in 11 clinical trials related to AD, Mild Cognitive Impairment, and Cerebral Amyloid Angiopathy.

However, recruitment and enrollment in such trials remain challenging (Grill and Karlawish, 2010). For example, in two specific studies at GMC, fewer than 5% of potential participants could be enrolled (26 out of 681 patient records reviewed). Recruitment is often a lengthy and resource-intensive process, but it can be improved through targeted strategies. Between 2018 and 2025, thanks to these efforts, GMC successfully enrolled 119 participants into clinical trials.

Beyond recruitment, participant retention is equally crucial (Grill and al., 2019). One key strategy implemented was a dedicated gathering for clinical trial participants, designed to offer a space for open discussion and shared experiences among participants and their study partners. At the end of the event, attendees completed a questionnaire assessing their satisfaction, motivation, and perception of the organization. Among the 33 participants, 95% were satisfied with the content, and 92% with the event's structure. Moreover, 94% stated that it strengthened their motivation to continue or participate in future trials.

These results highlight the value of structured strategies in dementia clinical research and their positive impact on recruitment, engagement, and retention of participants.

## **P66-D: Remote technologies in early stages of Alzheimer's disease: feasibility, usability and acceptance of an app-based cognitive training**

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**Background:** Treatment options for dementia due to Alzheimer's disease (AD) remain limited, with cognitive stimulation being one recommended intervention. We extend and adapt an existing tablet-based cognitive training (CT) programme and assess its feasibility, usability, and acceptance in the home- and care home-setting.

**Method:** In this non-randomized, observational study, 36 participants aged 70-95 are assigned to one of three study groups: healthy controls (HC; n=12), individuals with mild cognitive impairment (MCI; n=12), and individuals with AD (n=12). Participants undergo a neuropsychological assessment before engaging in a 2-week CT programme (10 daily 30-minute sessions, home or care-home setting) and are accompanied by a study partner (MCI and AD). Feasibility, acceptability, and usability are evaluated using half-structured group interviews in focus groups, in-app questions during the CT, and diaries. Furthermore, we assess feedback from study partners and the extent of support needed. The CT app is continuously optimised based on participants' feedback, starting with HC, followed by MCI and then AD groups.

**Result:** Data collection is ongoing. Results to date show a high adherence rate (>96%). Cognitive impairment is associated with longer learning times, while maximum level achieved is comparable in HC and MCI. Overall acceptability is moderate to high (5.14/7 points) with no difference in game ratings between men and women. Content analyses identified challenges related to progression speed, time allowed to solve tasks, keyboard use, instructions and wording, technical challenges, navigation, and app handling. Clearer instructions, visual cues, and simplified interaction were recommended and are being implemented to improve game experience and usability.

**Conclusion:** This study addresses a need for remote cognitive interventions with high feasibility, usability and acceptability for people with MCI and AD. The outcome of this study lays the groundwork for future controlled trials to assess efficacy.

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## **P67-D: Restoring mitochondrial homeostasis as a therapy for Alzheimer's disease**

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Mitochondrial dysfunction is a conserved feature of age-related diseases including neurodegenerative disorders. Accumulating evidence suggests that age-related mitochondrial impairment plays a fundamental role in the pathogenesis of Alzheimer's disease (AD), such as insufficient energy supply and excessive ROS production. Therefore, improving mitochondrial function may simultaneously target multiple AD pathologies. Here we report that a non-antibacterial tetracycline derivative, 9-tert-butyl tetracycline (9-TB), showed therapeutic effects in animal models of AD through activating the one of the mitochondrial quality control pathways – the mitochondrial stress response (MSR). In mouse models of AD, 9-TB mitigated cognitive decline, electrocorticography abnormalities, and amyloid accumulation. Further investigations into the underlying mechanisms of action will reveal how the improved mitochondrial population benefits brain function, thus paving the way for the development of mitochondria-targeting therapies for AD.

## P68-D: Targeting Neuroinflammation and Tau/APP Pathology via Intranasal Delivery of Azilsartan Medoxomil Nanoemulgel in AICl<sub>3</sub>-induced Alzheimer's Dementia Model

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**Background:** Cognitive impairment and dementia have become a global burden, distressing millions of elderly, accounting for progressive loss of neurons in the brain affecting higher multiple cortical centers, and impacting social life. The renin-angiotensin system and its receptors, widely distributed within the brain, offer potential to treat dementia via diminishing oxidative radicle generation, neuronal inflammation, and increasing blood-brain barrier (BBB) integrity. The present study delves into the formulation and optimization of thermoresponsive azilsartan medoxomil (AZL-M) loaded in situ nanoemulgel for targeted nose-to-brain delivery addressing the challenge of restricted entry of angiotensin receptor blockers (ARBs) to the brain due to low BBB permeability and validated through in vivo models.

**Methods:** A Box-Behnken design was used to optimize formulation parameters such as droplet size, gelation temperature, and drug release. The optimized nanoemulgel was characterized for physicochemical properties and evaluated for ex-vivo nasal mucosal toxicity, in-vitro cytotoxicity, and ROS reduction. In-vivo efficacy of intranasal application of the optimized formulation was assessed in an AICl<sub>3</sub>-induced Alzheimer's model.

**Results:** Formulation-F20 showed optimal gelation at 33.4°C, pH-6.21, droplet size of 160nm, 60.4% drug release in 8h, high permeation, and flux, with confirmed safety and cell viability. TEER studies confirmed the integrity of RPMI-2650 monolayers, and while apparent permeability values of AZL-M solution and nanoemulgel were comparable, the nanoemulgel exhibited significantly higher cumulative permeation across the nasal epithelial barrier. In-vivo studies showed that nanoemulgel significantly improved cognitive performance and neuronal survival. At the molecular level, AZL-M treatment led to a marked reduction in brain inflammatory cytokines TNF- $\alpha$  and IL-1 $\beta$ , along with downregulation of Alzheimer's-specific markers including phosphorylated tau, amyloid precursor protein, and NF- $\kappa$ B. Simultaneously, a significant upregulation of brain-derived neurotrophic factors indicated enhanced neurotrophic support and synaptic plasticity.

**Conclusion:** The intranasally delivered AZL-M-loaded nanoemulgel showed potential as a safe and effective therapy for Alzheimer's dementia by attenuating neuroinflammation and Alzheimer's pathology markers.

**Keywords:** azilsartan medoxomil; nanoemulgel; Alzheimer's dementia; neuroprotection; biomarker study

## P69-D: Targeting slow-wave sleep dynamics: closed-loop auditory stimulation as a translational tool for neurodegeneration

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Slow-wave sleep (SWS) alterations are critical features of neurodegenerative diseases such as Alzheimer's (AD) and Parkinson's (PD) disease, with disrupted slow-wave activity (SWA) exacerbating pathological processes. We developed and validated mouse closed-loop auditory stimulation (mCLAS) as a novel, non-invasive method to selectively target SWS and modulate SWA dynamics, providing a tool to address disease-specific impairments in neurodegeneration.

Our findings reveal that precise tracking of a 2 Hz component of slow waves, combined with phase-specific targeting, optimizes mCLAS efficacy. A 30° up-phase target produced significant 15–30% increases in SWA in AD (Tg2576) mice, whereas a 40° target enhanced SWA by 30–35% in PD (M83) mice. These parameters were tailored to maximize stimulation precision and enhance SWA across models, resulting in an adaptive modulation of pathological slow-wave characteristics. In AD mice, mCLAS reduced type I (global) slow-wave amplitude and slope while enhancing type II (local) slow-wave recruitment and synchrony, supporting sleep continuity and local network connectivity, while counteracting pathological sleep fragmentation. Contrastingly, mCLAS increased type I slow-wave incidence in PD mice, restoring pathologically impaired global synchrony and rebalancing 24-hour slow-wave dynamics while reducing type II prevalence toward healthy patterns. Overall, mCLAS selectively prompted the acute modulation of distinctive slow-wave types, boosting sleep homeostatic regulation mechanisms in both disease models. Moreover, preliminary results in the AD model suggest that mCLAS prevents behavioural deficits, reduces pathological protein deposition, and mitigates degeneration, highlighting the neuroprotective effect of SWS modulation via mCLAS.

These findings provide strong support for mCLAS as a translational tool for addressing sleep disturbances and underlying pathology in neurodegeneration. Hence, mCLAS may become the future cornerstone of SWA-based therapies for neurodegenerative diseases.

## **P70-D: Therapeutic potential of mitochondrial transplantation in a cellular model of tauopathy.**

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Tauopathies are neurodegenerative diseases characterized by an abnormal accumulation of the protein tau in cells, leading to significant neuronal death and cognitive impairment. An important feature of these tau-related diseases is the deficits in bioenergetic functions due to the impairment of mitochondrial integrity. Mitochondria are involved in many cellular processes, including adenosine triphosphate (ATP) synthesis. They are critical in the brain, which consumes much of the body's energy. It has been shown that mitochondrial dysfunctions precede cognitive deficits in these diseases. Therefore, mitochondria are considered a therapeutic target to prevent the development of brain disorders.

A new therapeutic approach is to consider mitochondria as the treatment itself with mitochondrial transplantation. This involves isolating healthy mitochondria and transplanting them into damaged organs or cells using various methods. Our project aims to investigate the therapeutic potential of mitochondrial transplantation in a cellular model of tauopathies.

We used the neuroblastoma cell line SH-SY5Y as recipient cells for the transplantation and the astrocytic cell line A172 as a donor of healthy mitochondria. Cellular and molecular biology tools, as well as fluorescence microscopy experiments, were used during the investigations.

We show that the functional integrity of isolated mitochondria is maintained after the isolation process, and that isolated mitochondria can enter the recipient cells. An optimal treatment concentration was determined, and an increase in cellular viability and bioenergetic functions of the healthy and tauopathy cellular model was observed. Moreover, an improvement in the neurite outgrowth has been detected in both cellular models.

Mitochondrial transplantation offers a new therapeutic approach in tauopathies by considering mitochondria as the treatment itself. Further investigations are needed to explore the cellular mechanisms underlying this phenomenon.

## **P71-D: Treatment-resistant depression in older adults: associated socio-demographic factors, dementia risk and therapeutic approaches**

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Treatment-resistant late-life depression (TRLLD) presents a major clinical challenge, affecting nearly half of older adults with major depression (1). This presentation synthesizes findings from three studies exploring: i) clinical and demographic factors associated with TRLLD, ii) factors associated with underlying dementia in individuals with TRLLD, and iii) current evidence on effective treatments.

A large retrospective cohort study of mental health records in South London (n = 8,171) revealed that TRLLD was present in 17.7% of individuals diagnosed with late-life depression, with higher prevalence among those with severe, psychotic, or recurrent episodes. Female sex, self-harm risk, and physical comorbidities—particularly hypertension—were associated with increased odds of TRLLD (2).

Among individuals with TRLLD, nearly one in four (22.9%) had co-occurring dementia. Factors associated with increased dementia risk included older age, female sex, Black or Asian ethnicity, cardiovascular and neurological comorbidities (e.g., hypertension, stroke, epilepsy), anxiety, apathy, and functional decline. In contrast, typical depressive symptoms such as low mood and guilt were negatively associated with dementia.

A systematic review of treatments for TRLLD identified 14 randomized controlled trials assessing both pharmacological (e.g., aripiprazole, venlafaxine, ketamine) and non-pharmacological interventions (e.g., rTMS, psychotherapy). Aripiprazole augmentation was found to be effective and well-tolerated. However, further large-scale trials are needed to assess the efficacy of treatments such as ketamine, rTMS, and psychotherapy (3).

These findings underscore the importance of personalized, multimodal management strategies for TRLLD, with close attention to physical health, cognitive function, and targeted interventions to improve outcomes and potentially reduce dementia risk.

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## Category: Care

### **P72-E: Exploring pain, anxiety and adverse effects associated with lumbar puncture in a memory clinic population: a prospective longitudinal study**

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#### **OBJECTIVE:**

To longitudinally evaluate pain, anxiety and adverse events (AEs) associated with lumbar puncture (LP) in older adults, and to investigate their association with patients' perceptions, clinical characteristics, and Alzheimer's disease (AD) cerebrospinal fluid (CSF) biomarker levels.

#### **BACKGROUND:**

LP is a common procedure in memory clinics to assess AD biomarkers and is generally considered safe and well-tolerated due to a low complication rate. However, patient discomfort before, during, and after LP may be underrecognized and underreported.

#### **METHODS:**

We prospectively recruited 109 consecutive Memory Clinic patients (mean age  $70.6 \pm 8.7$  years; 51% female) undergoing their first LP for cognitive assessment at the Geneva University Hospitals Memory Center (January 2024 – January 2025). Pain, anxiety, and AEs were assessed using structured surveys and the Beck Anxiety Inventory at four time points: before LP, immediately after, one hour post-procedure, and during a follow-up call 24-72 hours later. Categorical variables were analyzed with Cochran's Q test, non-parametric continuous variables were analyzed using Wilcoxon's or Friedman's tests, and multivariate regression was performed to examine associations between patient characteristics, CSF biomarkers, anxiety, AEs, and pain.

#### **RESULTS:**

Most participants reported minimal anxiety throughout the procedure. While mild headaches, back pain, and fatigue were common, severe AE occurred in only one participant (postdural puncture headache). AEs were not associated with cognitive status or CSF biomarkers, but were more frequent in females, suggesting a potential role for anatomical differences. Pain during LP was lower than patients expected, averaging less than 3/10, and post-procedural pain was low, strongly linked to the presence of adverse effects. Older patients reported less pain than younger patients. Patient satisfaction was high, with 80% of patients willing to undergo LP again.

#### **CONCLUSIONS:**

LP is well tolerated in older adults regardless of baseline anxiety, cognitive status, or AD CSF biomarkers. These findings support the use of LP for AD biomarker assessment in memory clinics.

## **P73-E: MemoApp: AI-Supported Telehealth for Personalized, Home-Based Dementia Care**

**Yakov Gerstein**

Center of brain research Medical University of Vienna

**Background:** MemoApp is an AI-supported telecare system designed to enhance home-based dementia care through smart, multilingual technology. While not yet fully AI-driven, MemoApp integrates assistive features that support remote engagement and daily routines for people with dementia at all stages. The system consists of therapeutic software in multiple languages, delivered via a personalized, autonomous smart screen that requires no digital literacy from the user. It enables structured cognitive stimulation and emotional support while connecting family caregivers and professionals remotely.

**Methods:** The system has been implemented in over 300 homes and care settings. Three longitudinal studies (2022–2024) assessed its clinical and practical impact, using mixed methods: caregiver-reported outcomes, professional evaluations, and system usage data.

**Results:** MemoApp improved routine adherence, orientation, and mood regulation. In early-stage dementia, it supported cognitive stabilization and reduced behavioral symptoms. Family caregivers reported lower stress, better communication, and greater emotional resilience. Use of the system helped delay institutionalization, and importantly, promoted greater independence and reduced reliance on others. Many users were able to remain safely at home for extended periods—an environment that often offers emotional safety and cognitive familiarity.

**Discussion:** MemoApp offers a unique model of culturally adapted, family-centered telehealth. It supports remote therapeutic engagement and personalized care, tailored to each individual's language, culture, and cognitive state. The platform continues to evolve through a collaborative design process involving professionals, caregivers, and real-world users. It was awarded a prestigious United Nations digital health innovation prize as the first technology specifically developed to support both people with dementia and their families.

**Future Directions:** MemoApp is currently expanding its AI capabilities, including conversational agents, passive behavioral monitoring, and predictive analytics to further support caregivers and clinical teams. Additional research initiatives are planned to evaluate long-term outcomes, optimize AI integration, and explore new use cases across different cultural and clinical contexts.

## **P74-E: Palliative and end-of-life care for dementia patients in a Swiss psychiatric hospital.**

**Stefanie Steininger**

Clenia Klinik Schlössli, Oetwil am See

**Importance:** With the increasing prevalence of dementia syndromes and polymorbidity, palliative care (both early and end-of-life care) is becoming an increasingly important issue for the quality of life and treatment of patients with dementia. Therefore, geriatric psychiatry faces new challenges in implementing palliative care to optimise treatment options for patients with dementia, especially in an inpatient setting.

**Aim:** How can palliative care be integrated into inpatient geriatric psychiatry, which medications are feasible and where are the limitations?

**Design, setting and participants:** A total of 211 patients were admitted to a neuropsychiatric ward in 2024, with a focus on dementia syndromes, BPSD and delirium. An early palliative care plan was developed in 25%. Four patients received end-of-life palliative care.

**Results:** Intensive family care, spiritual care, development and implementation of an early palliative care plan, and close medical and nursing care, including bolus medication administration via subcutaneous catheter at the end of life, were defined as feasible. With regard to medication, the recommendations of Palliativmedizin Ostschweiz were considered feasible for the most part. Patients who required a specialised palliative care setting for pain control, dyspnoea or i.v. sedation could not be managed.

Overall, the introduction of palliative care was appreciated by patients and their carers.

**Conclusion:** Palliative care, knowledge and management are essential in geriatric psychiatry. Early advance care planning and end-of-life care may be feasible in an inpatient setting, with limitations. However, there are serious limitations: Palliative care in geriatric psychiatry can never be an alternative to specialist inpatient palliative care. But it can be a valuable addition. Palliative care in psychiatry is a taboo that is long overdue. It represents an evolution in geriatric psychiatry and should be given greater consideration in future care planning.

## **P75-E: Telemedicine for Older Adults: A Pilot Study on the Usability and Acceptability in Remote Cognitive Assessment**

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### Background:

With an aging population, cognitive decline and dementia present significant healthcare challenges. Accurate diagnosis and early intervention are crucial, yet access to specialized dementia screening clinics remains limited - particularly in rural and remote areas. Telemedicine offers a promising avenue to expand access to early cognitive assessments. This pilot study explores the subjective experiences of older adults undergoing remote cognitive testing, focusing on how they perceive and interact with digital technology in the context of person-centered dementia care. It also examines clinicians' perspectives on the platform's usability and the quality of remote interactions.

### Methods:

A secure videoconferencing platform was developed to administer a range of standardised neuropsychological assessments remotely. The study captures the perspectives of older adults completing the assessments and clinicians delivering them. Usability and acceptability were evaluated using 10-point Likert scale questionnaires, supported by structured qualitative interviews with clinical staff.

### Results:

Preliminary findings from 10 participants indicate high satisfaction with the remote assessment experience, including ease of use (m=8.33), video quality (m=8.39), and audio clarity (m=8.19). Clinicians, however, noted lower satisfaction due to technical setup issues (m=4.13) and challenges in communication with older individuals through the platform (m=5.5). Qualitative insights are currently being collected and will undergo thematic analysis upon completion of data collection in July 2025.

### Conclusion:

These early findings suggest that telemedicine is a promising and acceptable approach for cognitive assessment among elderly, particularly in areas with limited in-person services. While participants reported positive experiences, clinician feedback highlights areas for improvement. Enhancing platform usability and interaction quality will be critical to supporting the integration of remote cognitive assessments into routine care and advancing equitable access to dementia services across diverse populations.

## **P76-E: The language of care: what metaphors reveal about the experiences of dementia (in)formal caregivers**

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### **Background and Objectives:**

In Ticino, the Italian-speaking region of Switzerland, most people with dementia live at home, with informal and formal caregivers playing a critical role in daily care. Metaphorical language is often used to articulate the complex nature of care, offering valuable insights into the lived experiences of caregivers. This study explores how caregivers in Ticino spontaneously use metaphors in their narratives to conceptualize dementia and their role.

### **Research Design and Methods:**

We conducted six focus groups with caregivers of people with dementia (N=6 formal, N=13 informal) as part of the Swiss adaptation of the World Health Organization's iSupport for dementia program. A qualitative content analysis was performed focusing on metaphors' semantic and linguistic complexity and contextual meanings. Metaphors were categorized into three themes: (1) about dementia, (2) about caregiving, and (3) about the caregiver-person with dementia relationship.

### **Results:**

Caregivers frequently framed people with dementia as "children" or employed natural elements to depict their burden. Metaphors revealed different caregiving perspectives: some emphasized an individualistic approach aimed at independence while "patching" problems or "drowning" in challenges; others reflected a community-centered moral dedication view, like the metaphor of a "mission"; others captured the complex dynamics of power and dependency in the caregiver-person with dementia relationship.

### **Discussion and Implications:**

Unlike commonly cited metaphors in dementia literature, metaphors used by caregivers in Ticino were deeply rooted in local context. Overall, metaphors provided a multifaceted view of caregiving, illuminating tensions between self-care and care for others. Some metaphors foster an empathetic approach to care, while others (i.e., infantilization) risk reinforcing stigma or idealizing self-sacrifice. This study highlights the importance of reflecting on caregiving language in training and support programs to improve mutual understanding, challenge stigma, and promote person-centered approaches.

## **P77-E: Toward Measurable Dementia Competence: A Delphi Study to Develop Indicators for Quality Dementia Care**

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**Background:** Dementia imposes a significant burden on healthcare resources, driven by the need for ongoing, intensive support as the condition advances. This burden is further compounded by additional challenges such as behavioral and psychological symptoms of dementia (BPSD) and delirium, which often contribute to more complex and resource-intensive care trajectories. Effective dementia care requires timely recognition and tailored management of symptoms such as BPSD and delirium. By focusing on tertiary prevention, it is possible to prevent escalation, enhance quality of life, and reduce strain on healthcare resources. Despite the critical role of effective dementia care, the absence of clear indicators to assess its quality hinders efforts to evaluate outcomes and drive systematic improvements across care settings.

**Methods:** Clinicians, advanced practice nurses, dementia care specialists and researchers practicing in either the canton of Bern or Zurich will be recruited for this Delphi study. The development process is guided by the National Dementia Platform, the German S3-Guidelines on Dementia and the Swiss Recommendations for the Diagnosis and Treatment of BPSD. The newly developed indicators will undergo validation through theoretical examinations and observation processes of individuals engaged in dementia care.

**Results:** In total, 20 experts will be recruited to participate in the Delphi study, with the objective of establishing indicators for 18 pre-existing criteria derived from the above mentioned sources. Preliminary results are anticipated by the fall of 2025.

**Conclusion:** Establishing indicators of competent dementia care is critical for improving care quality and system efficiency. These indicators enable the healthcare system to track performance, identify areas for improvement, and implement targeted interventions that align with best practices. By operationalizing complex care needs into measurable outcomes, driving continuous quality enhancement and ensuring person-centered care for people living with dementia.

## **P78-E: Unlocking the Potential of Electronic Health Records for Dementia Research: Insights from the Clinical Record Interactive Search (CRIS) Platform**

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The application of large-scale electronic health record (EHR) data is set to be one of the most transformative developments in health research over the next decade. Advances in data linkage, natural language processing, and artificial intelligence are accelerating the extraction of clinically meaningful insights from routinely collected healthcare data. EHRs generate unprecedented volumes of information on real-world clinical care, offering opportunities to address questions of direct clinical relevance—particularly in populations hard to recruit into de novo cohort studies or trials, such as some people with dementia.

The Clinical Record Interactive Search (CRIS) platform, established in 2008, provides research access to anonymised records from the South London and Maudsley NHS Foundation Trust, one of Europe's largest mental health and dementia care providers. CRIS supports ethically approved, secure use of structured and unstructured clinical data, enabling studies on over 20,000 patients with dementia. More than 50 dementia-related peer-reviewed publications have emerged from this resource, addressing diverse epidemiological and service-related questions.

Findings from CRIS include evidence that loneliness, higher predicted brain age, and incident late-life depression are linked to increased dementia risk. Certain medication classes (such as anticholinergics and sedatives) are associated with higher hospitalisation and mortality risk, while bladder antimuscarinics crossing the blood–brain barrier are linked to faster cognitive decline than non-crossing agents. Other work has identified clinical markers of underlying dementia in people with treatment-resistant late-life depression.

Although challenges remain, particularly fragmentation of information across specialties, the potential for EHR-based research to inform dementia care pathways is substantial. CRIS is continually expanded with new natural language processing applications (e.g. identifying core symptoms of dementia with Lewy bodies) and data linkages (e.g. with social care), generating insights to improve prevention, diagnosis, and treatment, and bridging the gap between research and real-world practice.

## Category: Prevention

### **P79-F: An integrated action plan for dementia prevention in Geneva: the cognitive pillar of the Swiss Brain Health plan**

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Dementia prevention is a critical public health challenge, profoundly impacting individual quality of life, family well-being, and societal costs. The World Health Organization recognizes dementia prevention as a public health priority; however, standardized procedures to address this priority remain limited. At the Geneva Memory Center of Geneva University Hospitals, we developed and implemented an integrated plan to promote cognitive health and prevent cognitive decline, including community education, general practitioner involvement, and specialized care initiatives for dementia prevention. The first component, the Prevention Memory Workshop ("Atelier mémoire de prévention"), provides education, social and cognitive stimulation for the general public. This initiative includes structured activities aimed at increasing awareness about brain health and providing practical recommendations and tools for dementia prevention. The second component, the Lemanic Program on Cognitive Impairment and Dementia ("Cours Lémanique sur les Démences et les Troubles Cognitifs"), engages general practitioners as key stakeholders, promoting best practices for dementia prevention in the Lemanic region and French-speaking Switzerland. The third component, Brain Health Services for dementia prevention (dBHS), provides a comprehensive secondary prevention approach. dBHS offers risk assessment, risk communication, and personalized strategies for cognitively unimpaired individuals at risk of developing dementia. Utilizing advanced tools, dBHS identifies individuals at increased dementia risk and develops tailored intervention plans incorporating lifestyle modifications and biological interventions. This abstract describes the development and implementation of these initiatives, highlighting comprehensive dementia prevention strategies. These programs may serve as models for adoption in other European countries, addressing the global challenge of dementia prevention.

## **P80-F: Enhancing Cognitive and Physiological Health in Older Adults Through Social Interaction**

**Marc Züst**

University Hospital of Old Age Psychiatry and Psychotherapy, UPD Bern

Sleep and loneliness are increasingly recognized as modifiable risk factors for dementia. Positive social interactions have been linked to better sleep, cognitive function, and physiological health. This project tests the hypothesis that engaging older adults in social activities, specifically collaborative board game nights using the award-winning game Dorfromantik, can enhance sleep quality, memory, and plasma-based biomarkers of brain health.

The study will follow a between-subject design comparing collaborative versus solo game play. Outcome measures include polysomnography, episodic memory testing, high-density EEG synchrony between players, slow-wave–spindle coupling during sleep, and biomarker levels (saliva oxytocin; plasma A $\beta$ , pTau, GFAP, NfL). Social bonding will be assessed via self-report and standardized video analysis.

A parallel rodent study is envisioned, using group versus single housing and behavioral assays to explore learning, mood, and social behavior. This translational approach could shed light on the neural and biochemical mechanisms linking social engagement to sleep and brain health.

If successful, this project could provide a low-cost model for social-based sleep enhancement with real-world public health applications, including integration into care facilities and community programs. Further innovation may arise from digital tools to support and monitor such interventions.

## **P81-F: Enhancing Motivation for Dementia Prevention: A Digital, Value-Based Just-in-Time Adaptive Intervention Framework**

**Esther Brill, Stefan Klöppel**

University Psychiatric Services (UPD) Bern

### **Background**

Dementia constitutes a growing global public health concern, underscoring the urgent need for effective and sustainable preventive strategies. Multidomain lifestyle interventions, encompassing physical and cognitive training, dietary modifications, and social engagement are commonly recommended to mitigate dementia risk. However, long-term maintenance of behavioral changes requires strong motivational and volitional processes. Value-congruent behaviors enhance intrinsic motivation through meaningful and stable behavior-outcome associations. Despite the efficacy of well-structured lifestyle-interventions, long-term adherence remains optimizable, with fewer than half of participants completing all components.

### **Methods**

We designed a digitally-embedded value-based motivational framework, integrating smartphone-based momentary assessments, reminders, and just-in-time adaptive interventions (JITAs). A feasibility study (n = 15) was conducted in older adults with subjective or mild cognitive impairment to evaluate the acceptability and usability of these digital tools. Our framework is designed to align individual values with lifestyle goals, employing motivational interviewing and goal-setting techniques. After initial implementation as a manualized clinical consultation in a memory clinic setting, we now evaluate the effects of smartphone-delivered personalized, value-based communication styles compared to neutral statements on the intended adherence to dementia preventive behaviors.

### **Results**

The feasibility pilot highlights that smartphone-based JITAs are both acceptable and well tolerated among older adults with cognitive concerns. The digital interventions demonstrated good adherence and high user acceptability. Clinical observations indicate that value-based motivational approaches may enhance participants' intention to adhere to recommended lifestyle changes. The evaluation of the effects of positively-framed, value-based digital messages on lifestyle adherence is currently underway.

### **Conclusion**

Digitally delivered value-based motivational approaches and positively framed communication show considerable promise in supporting sustained engagement in dementia-preventive lifestyle behaviors. These interventions are clinically relevant, scalable and resource-efficient, making them well-suited for broader public health implementation. By targeting long-term behavior change, this framework may contribute to healthy aging and inform future strategies for dementia risk reduction.

## **P82-F: Implementing a Primary Dementia Prevention Program in Geneva: Feasibility and Preliminary Outcomes**

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As the global population ages, dementia becomes a critical public health concern. According to the 2019 Global Burden of Disease Study, 50 million people worldwide currently live with dementia—a figure projected to reach 152 million by 2050. In response, the World Health Organization has prioritized dementia prevention. Recent evidence suggests that up to 45% of dementia cases are attributable to fourteen modifiable risk factors, including social isolation, low levels of education, physical inactivity, and cardiovascular health issues, highlighting the potential of targeted preventive interventions.

This study proposed a structured primary prevention program for the general population aged from 50 and above. The intervention included seven interactive workshops aimed at raising awareness of dementia prevention strategies, promoting evidence-based lifestyle changes, and fostering community engagement. The workshops focused on three core pillars: continued education, cognitive training, and social engagement. Sessions covered essential aspects of aging, including distinctions between physiological and pathological aging from cognitive, psychological, and physical perspectives, along with the role of physical activity and nutrition.

To evaluate participant satisfaction and perceived impact, a questionnaire was completed after the workshop series. Key domains included feasibility, knowledge acquisition, cognitive self-perception, and motivation for lifestyle changes. Follow-up assessments at 3 and 9 months used the same questionnaire to evaluate longer-term outcomes.

Among 41 participants, baseline data showed 94% satisfaction with the workshop's feasibility, and 98% found the content informative for dementia prevention. Additionally, 88% reported reduced concern about age-related memory decline, and 85% indicated the program supported changes in their daily life. Abstentions and negative responses (1% to 13%) were primarily linked to the program's limited duration and technical difficulties with computerized cognitive training.

This pilot initiative demonstrates the feasibility of a structured, evidence-based primary prevention program and its potential to enhance awareness and empower participants with tools to support dementia prevention.

## **P83-F: Preventing cognitive decline using portable, non-invasive sleep enhancement.**

**Korian Wicki**, Marina Wunderlin, Marc Alain Züst

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Recently, disturbed slow wave sleep (SWS) has been identified as an early, modifiable risk factor for dementia. SWS is crucial for memory and metabolic clearance functions, and lack of SWS causes these critical functions to suffer, which in turn worsens cognitive decline. A vicious cycle forms between cognitive decline and loss of SWS. Improving SWS could be a way to break this cycle by providing the much-needed opportunity for the brain to recuperate and ameliorate cognitive decline. We aim to enhance slow wave activity in older adults using phase-locked auditory stimulation (PLAS). Our laboratory-based results show that the magnitude of the physiological response to PLAS predicts improvement of memory functions and metabolic clearance. However, larger, long-term studies in an ecologically valid setting are needed to assess the efficacy of PLAS for the improvement of sleep, memory, and metabolic clearance with the goal of preventing cognitive decline. Laboratory-based studies quickly become economically and logistically unfeasible to achieve this goal.

We propose a blinded, sham-controlled cross-over study utilizing home-use devices to study the effect of PLAS on memory functions in 60 older adults with cognitive impairment. Participants will undergo real- and sham-PLAS in the comfort of their own homes across a 12-week study period. Cognitive performance will be assessed using engaging "serious games", and blood will be sampled before- and after each experimental period to test levels of dementia-related biomarkers and their response to PLAS.

We expect PLAS to enhance sleep, leading to downstream effects on memory performance and metabolic clearance. Using a novel approach allowing brain-age estimation from sleep-electrophysiology, we hypothesize to see a "rejuvenating" effect of PLAS, restoring an electrophysiological profile typically seen in younger brains.

This study could pave the way for PLAS-capable home-use devices as an affordable, non-invasive tool to combat cognitive decline and could lead to novel preventative applications for memory clinics, relieving their clinical burden and improving public health.

## **P84-F: Slow wave–spindle coupling during deep sleep is uniquely linked to Plasma Amyloid- $\beta$ levels in Older Adult**

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Slow wave activity, the signature of deep sleep, has consistently been linked to amyloid-beta ( $A\beta$ ), a pathophysiological marker of neurodegeneration. Less is known about how  $A\beta$  relates to specific microstructural processes within deep sleep, such as the coupling of slow waves and spindles, where better functioning reflects younger age, increased memory, and less brain atrophy.

47 older adults (agemean = 70.5 (0.68)) ranging in cognitive functioning completed one adaptation and one baseline night. A subsample (n=39, agemean = 70.5 (0.74)) additionally underwent a three-night acoustic stimulation intervention to boost slow wave activity. Blood samples post-baseline and post-intervention were analyzed for  $A\beta$  1-42/1-40-ratio.

Irrespective of cognitive functioning levels, slow wave–spindle coupling was the best predictor for baseline  $A\beta$ , better than slow wave activity, age or cognitive functioning. Specifically, better  $A\beta$ -levels were linked to a coupling physiology resembling a younger brain. While intervention-induced increases in slow wave activity were linked to a beneficial  $A\beta$ -response across all cognitive levels, increases in slow wave–spindle coupling benefited  $A\beta$ -response exclusively in cognitively impaired individuals.

Our results suggest a link between SW–spindle coupling and  $A\beta$  that goes beyond slow wave activity. This hints towards a potential specific function of SW–spindle coupling related to the early pathophysiology of neurodegeneration.

## **P85-F: The Brain Health Registry: A Resource for Swiss Research on Alzheimer's and Dementia**

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One promising method to enhance the recruitment of volunteers in memory clinics is the use of online potential participant registries. These registries facilitate access to clinical trials for many interested people, while also reducing costs and shortening enrollment times (Harris and al., 2012; Grill and al., 2014; Watson, Ryan, Silverberg, Cahan & Bernard, 2014). Online registries represent an effective strategy to face the main barrier for research studies on dementia: the recruitment and enrollment of participants (Grill and Karlawish, 2010). Indeed, it is very difficult to reach the recruitment target on time. Most studies fail in their recruitment mission, which considerably slows down the research process and can also impact internal validation as well as the generalization of results (Grill and Galvin, 2014). These long phases of participant selection and enrollment also generate high costs. However, the major challenge for research on Alzheimer's disease (AD) and other types of dementia - finding a curative treatment- remains, and time continues to pass. The recent approval of anti-amyloid monoclonal antibody therapies marks a turning point, leading to an increase in the number of clinical trials. In this context, the Brain Health Registry established in Switzerland represents a valuable resource for future research on Alzheimer's disease and other dementias by facilitating the identification and recruitment of suitable participants.

## **P86-F: The evolving potential for dementia prevention in Switzerland: population attributable fractions of risk factors over time**

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It is estimated that modifiable risk factors (RFs) account for approximately 45% of dementia cases worldwide. While several studies have examined the extent to which these RFs contribute to dementia incidence in other regions, such as Brazil, Denmark, China, USA, Switzerland's specific context has not been investigated. This is of particular interest because recently it has been shown that dementia incidence is declining in many high-income countries. Therefore, we aimed to calculate the population attributable fraction (PAF) in the Swiss population who have access to high-quality health care system to inform effective dementia prevention strategies. We will use the Swiss National Health Survey, a nationally representative dataset, in which potentially modifiable dementia RFs were collected every five years from 1992 to 2022. The PAF for each risk factor (RF) will be estimated based on its prevalence and the associated relative risks from prior meta-analyses. We will adjust for the communality between RFs and calculate overall weighted PAF, focusing on variations across cantons and over time.

Result: We expect that the PAF for dementia in Switzerland will show how the potentially modifiable RFs have contributed across the years to dementia incidence. We anticipate that the overall PAF might be lower than in low-income countries, reflecting Switzerland's high quality of health care system. In addition, due to the lifestyle changes in Switzerland, we expect to see a decrease in weighted PAF between 1992 and 2022. The harmonization of the data across years is ongoing and the results will be presented at AAIC in July 2025. This study is essential for understanding how potentially modifiable factors contribute to dementia risk in Switzerland. By identifying the contribution of the RFs, we will reveal the potential for dementia prevention in the Swiss context. These findings will offer crucial evidence to guide public health policies and targeted interventions, helping to reduce the burden of dementia in Switzerland.

## Category: Behavior and cognition

### **P87-G: 24-hour movement behavior of institutionalized people with moderate to major neurocognitive disorders**

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Sedentary lifestyles accelerate brain ageing, while regular physical activity can mitigate cognitive impairment and reduce dementia risk (Tari et al., 2025). We investigate and compare 24-hours movement behaviors in residents with moderate to major neurocognitive disorders (MNCD) against guidelines (Ross et al., 2020).

Residents with MNCD (Sonnweid AG (Wetzikon (CH)) were screened on "major neurocognitive disorders" according DSM-5® (APA, 2013), and Mini Mental State Examination (MMSE)  $\geq 5-26$  (Trivedi, 2017). Following informed consent assessments ran from September 2024 onwards. Outcomes include the amount of physically activity (PA) and sedentary behavior (SB) over 24-hours.

Out of 44 residents approached, 8 declined participation, 3 presented with MMSE  $< 5$ , and 1 person dropped out for health reasons. Data of 32 residents (13 male) show participants had a Mini-Mental Status Exam of median (IQR) 17.5 [13.75-20.0] points. SB median (IQR) was 12.98 [11.03-15.27] h/day, median (IQR) light PA 3.33 [2.49-4.18] h/day, median (IQR) moderate PA 0.19 [0.06-0.36] h/day, median (IQR) vigorous PA 0 [0-0.004] h/day, total sleep time median (IQR) 4.88 [3.85-7.19] h/day, sleep latency median (IQR) 0.31 [0.25-0.34] h/day, wake up after sleep onset median (IQR) 3.41 [2.79-4.41] h/day. Sleep efficiency median (IQR) was 61 [54-69] %.

This study gives quantified insights into PA, SB, and sleep of Swiss residents with MNCD.

Compared with guidelines-based recommended PA (21.5 min/day moderate to vigorous activity), sleep (getting 7 to 8 hours of good-quality sleep) and SB (8 h/day or less) (Ross et al., 2020) our participants show unfavorable values. This warrants research into how long periods of sitting can be broken up and PA & sleep can be improved through dedicated programs.

## P88-G: Beyond "Dementia": Reimagining Nomenclature for Cognitive Health

**Andra Bria**

CAS in Brain Health University of Bucharest, Social Science

Language shapes perception, and nowhere is this more evident than in medical terminology. The term "dementia"—derived from Latin meaning "away from" mind—carries centuries of stigma, fear, and implications of irreversible decline. This linguistic framing influences how society views these conditions, how healthcare professionals approach treatment, and critically, how diagnosed individuals perceive their own futures.

While medical science has advanced our understanding of neurodegenerative conditions, recognizing spectrums, subtypes, and potential interventions, our terminology remains rooted in outdated paradigms. This talk explores the psychological and social implications of the term "dementia" and proposes a framework for developing language that acknowledges reality while preserving dignity and hope.

Drawing from research in neurolinguistics, health psychology, and patient-centered care, I'll examine how terminology affects treatment engagement, caregiver expectations, research funding, and public health messaging. Case studies from other medical fields that have successfully updated terminology (e.g., from "mental retardation" to "intellectual disability") provide valuable insights.

I propose a pathway toward terminology that emphasizes brain health rather than deficit, accurately reflects our evolving understanding of these conditions as potentially modifiable, and empowers rather than diminishes those affected. Potential alternatives include "neurocognitive condition," "cognitive health challenge," or condition-specific terms that reflect underlying pathology rather than symptoms.

This linguistic evolution must balance scientific accuracy with psychological impact. By reconceptualizing these conditions through language, we can reduce stigma, encourage earlier diagnosis, promote prevention efforts, and maintain human dignity throughout the process. The words we choose don't just reflect our understanding—they shape it. As our knowledge evolves, so too should our language, creating space for both medical reality and human hope.

## **P89-G: Gender matters in the Association Between Subjective Cognitive Complaints and Memory in Healthy Ageing**

**Marta Garo-Pascual<sup>1</sup>, Cristina Ramponi<sup>1</sup>, Alexia Candal-Zürcher<sup>1</sup>, Bogdan Draganski<sup>1</sup>**

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Subjective cognitive complaints (SCC) are common in older adults, but their value as a marker of the prodromal stage of Alzheimer's disease is debated due to inconsistent associations with objective cognitive performance and stronger links with depressive symptoms. Given gender differences in Alzheimer's disease and depression, this study examined gender-specific associations between SCC and episodic memory in cognitively healthy older adults. SCC were assessed using the Questionnaire of Cognitive Complaints (QPC, Questionnaire de Plainte Cognitive), and episodic memory using the free delayed recall score of Free and Cued Selective Reminding Test (FCSRT) in a sample of 870 cognitively healthy, community-dwelling adults aged  $\geq 65$  years (mean [SD] = 70.9 years [4.5]) from the CoLaus|PsyCoLaus cohort study. Regression analyses were conducted with and without adjustment for psychosocial well-being (GAF) and depressive symptoms (CES-D). Women ( $n = 515$  [59.3%], 71.0 years [4.4]) showed better episodic memory performance than men (70.8 years [4.5]), having fewer years of education, lower psychosocial well-being, and higher depressive symptom scores. The number of SCC did not differ between genders. Across the whole sample, a higher number of SCC was associated with poorer episodic memory performance. When stratified by gender, this negative association was significant only in men, while no association was observed in women. Examination of individual SCC items revealed that "Impression of memory change" was the only item showing significant gender interaction. Among men, those reporting this complaint performed worse on episodic memory than non-complainers, whereas no such difference was found among women. These findings highlight the importance of incorporating a gender perspective in the evaluation of SCC to better understand the preclinical phase of Alzheimer's disease. The results suggest that SCCs, as measured by the QPC, are associated with episodic memory performance in men but not in women, potentially overlooking age-related or pathological changes in women.

## **P90-G: Memories Fade, Traces Remain: Neural and Behavioural Correlates of Forgotten Episodic Memories Found After 6 Months with 7T fMRI**

**Konstantinos Ioannis Zervas**, Tom Willems, Shawn Hiew, Katharina Henke

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Episodic memories fade rapidly after learning, with the majority forgotten within 24 hours, yet we hypothesized that memory traces (engrams) of the forgotten information persist within the human brain's episodic memory system. We investigated the long-term fate of 96 newly learned face-object associations over a six-month period in 40 young, healthy participants. Using 7T whole-brain fMRI, we tracked memory traces as they are formed and retrieved 30 minutes, 24 hours, one week, and six months later. During each retrieval trial, participants rated their memory confidence. Responses rated as 'guessed' were classified as forgotten. At 30 minutes post-encoding, 33% of associations were forgotten; this slightly decreased to 31% at 24 hours, before rising to 38% at one week and 46% at six months. Although retrieval accuracy for guessed responses remained at chance across all intervals, underlying memory traces persisted within the episodic memory network, including hippocampal and prefrontal regions. Both their reactivation and hippocampal-prefrontal connectivity significantly correlated with guessing retrieval accuracy. Memory traces of forgotten associations closely matched the location and shape of those supporting consciously accessible memories, but they were thinner and showed greater changes over time. In contrast, traces associated with accessible memories remained more stable and showed strong recruitment of the neocortex as early as 30 minutes following encoding. These findings suggest that ostensibly forgotten memories persist in the brain although they are no longer accessible to conscious awareness. Thus, forgetting may reflect a loss of conscious access rather than a loss of the underlying information itself.

## P91-G: Metacognitive impairment in Subjective Cognitive Decline: Evidence from a Memory Clinic Population

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### 1. Introduction

Subjective Cognitive Decline (SCD) refers to the self-perception of cognitive difficulties despite normal performance on standard neuropsychological tests (Jessen et al., 2020). SCD is associated with an elevated risk of future cognitive impairment and dementia. This study aimed to examine metacognition in cognitively unimpaired individuals with and without SCD (Ribaldi et al., 2021).

### 2. Materials

Subjects completed a neuropsychological test battery and a prospective-retrospective memory task consisting of a lexical decision phase followed by a recall phase.

The task yielded measures of performance prediction (Judgments of Learning, JoL) and metacognitive accuracy (concordance between JoL and actual performance): assessed before the task (predictive) and after (postdictive) (Cauvin et al., 2019).

### 3. Methods

This study included 139 cognitively unimpaired individuals from the Geneva Memory Center cohort. SCD (n=80) self-reported complaints without objective deficits; volunteers (n=59) referred no complaints or deficits. All were free from neurological or psychiatric comorbidities. They completed a metacognitive task.

### 4. Results

SCD were significantly older (68 years [62 – 74]) than volunteers (62 years [57 – 68],  $p=.003$ ). No differences occurred in overall task accuracy components (prospective:  $p=.468$ ; retrospective:  $p=.415$ ). However, SCD showed significantly lower predictive JoL in both the prospective ( $p=.005$ ) and retrospective ( $p=.033$ ) components. In contrast, postdictive JoL scores did not differ between groups (prospective:  $p=.135$ ; retrospective:  $p=.400$ ).

In the prospective memory task SCD showed reduced prospective metacognitive accuracy ( $p=.034$ ), while no differences were observed in postdictive accuracy ( $p=.106$ ).

### 5. Discussion

SCD show a reduced predictive JoL and predictive metacognitive accuracy in prospective memory. This did not occur after task execution, suggesting a possible metacognitive realignment. These evidences lead to hypothesize impairment of predictive metacognition as a potential early marker of cognitive decline.

### 6. Conclusion

SCD individuals have impaired predictive metacognitive accuracy despite similar performance, suggesting that this specific impairment may represent an early marker of cognitive decline.

## **P92-G: Neural Traces of Forgotten Memories Persist in Humans and are Behaviorally Relevant**

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For a long time, forgetting has been taken as the dissipation of the neural memory traces (engrams). However, recent engram research in mice, however, suggests that the engrams of forgotten memories do persist. This raises the question whether engrams underlying human episodic memories also persist despite forgetting? And do forgotten memories influence human behavior implicitly? To address this question, 40 men and women learned 96 face-object pairs. Using high-resolution functional magnetic resonance imaging at 7 tesla we mapped the fate of the 96 memories at the systems level from learning to a 30-minute and onward to a 24-hour memory test. Upon each retrieval attempt, participants indicated whether they remembered or forgot the memory. Univariate and multivariate analyses of the functional brain data revealed that the engrams of forgotten memories remain implemented in the episodic memory network and continue to influence the accuracy of guessing responses at test. The engrams of forgotten memories were implemented more deeply within bilateral hippocampus overnight, while consciously accessible memories were neocorticalized overnight. The engrams of both consciously accessible and inaccessible (forgotten) memories were shifted by overnight consolidation within right hippocampus and anterior cingulate gyrus such that pattern dissimilarities supported correct retrieval responses. We provide strong evidence that forgotten human episodic memories remain implemented in the episodic memory network and continue to influence behavior implicitly. Contrary to what traditional models of memory, conscious accessibility is not a prerequisite for episodic memory.

### **P93-G: Preliminary data on power spectral analysis of resting-state EEG in cognitive decline and healthy aging**

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Mild cognitive impairment (MCI) is the transitory stage between normal aging and dementia, affecting 10-20% of adults aged 65 and older. Despite its prevalence, the mechanisms underlying the MCI stage of cognitive decline remain largely unclear. Resting-state electroencephalography (EEG) power spectral analysis is a widely used technique to investigate functional brain changes associated with cognitive decline and aging. Previous research indicates that Alzheimer's Disease (AD) is characterized by increased power in slow-wave (delta and theta) and decreased power in fast-wave (alpha and beta) frequencies. Similar, though less consistent, spectral patterns have been observed in individuals with MCI. In contrast, healthy aging is generally associated with reduced slow-wave and alpha activity, alongside increased beta power. In this preliminary study, we performed a power spectrum analysis of resting-state EEG recordings from three groups: individuals with MCI, healthy older adults, and healthy younger adults. High-density EEG recordings (257 channels) were obtained from 30 participants in total (N=10 per group) during a 5-minute resting-state with eyes closed and analyzed using the Welch method across frequencies between 1 to 70 Hz. Preliminary uncorrected results revealed a reduction in alpha power in both MCI and healthy older adults over occipital and temporal regions, consistent with typical age-related neural changes. MCI patients also showed increased theta power compared to healthy controls over frontal and right temporal regions, indicating EEG slowing. Interestingly, beta power increased in MCI patients compared to healthy controls over frontal, parietal, and occipital regions, in contrast to previously reported reductions in AD. These findings suggest that early cognitive decline in MCI may primarily involve increases in slow-wave activity, while decreases in fast-wave activity may occur later during progression toward AD.

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