SynaDeg
PRE-DIAGNOSTIC EARLY SYNAPTIC DISTURBANCES IN NEURODEGENERATIVE DISEASES

JPND research
EU Joint Programme – Neurodegenerative Disease Research

SynaDeg
Prediagnostic early synaptic disturbances in neurodegenerative diseases

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External collaborator: Barbara Borroni, University of Brescia (UNIBS), Italy

Patient organizations: The Alzheimer Society of Finland (**Muistiliitto**), Finland; Italian Frontotemporal Dementia Association (**AIMFT**), Italy

Project duration: 2022-2025

UNIVERSITY OF EASTERN FINLAND
UNIVERSITY OF OULU
HOSPITAL DE LA SANTA CREU I SANT PAU
UNIVERSITAT AUTÒNOMA DE BARCELONA
DZNE Deutsches Zentrum für Neurodegenerative Erkrankungen in der Helmholtz-Gemeinschaft
UNIVERSITY OF GOTHENBURG
UNIVERSITÀ DEGLI STUDI DI BRESCIA
Muistiliitto Minnesförbundet
associazione AIMFT FRONTOTEMPORALE

SynaDeg aims

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WP1: Identification of **early physiological and synaptic changes**, which could improve the early diagnosis of **FTD** and **DLB** by ***i)*** pinpointing **specific clinical symptoms related to physiological disturbances** (*e.g.*, altered behaviour and autonomic functions) and ***ii)*** detecting **neurotransmitter system alterations** (by transcranial magnetic stimulation, TMS) predicting synaptic dysfunction and neurodegeneration

WP2: Discovering **new CSF or blood-based biomarkers of early synaptic dysfunction** in well-characterised cohorts of FTD and DLB patients

WP3: Characterisation of specific **pathological and functional alterations underlying synaptic dysfunction and their mechanisms** in *post-mortem* brain samples and patient-derived iPSC-neurons from FTD and DLB patients

WP4 & 5: Strengthening **collaboration between research community, health care professionals, and patient organisations (PO)** to promote efficient dissemination of SynaDeg results to different stakeholders and to establish ethical and best practices for patient recruitment for clinical research

Tackling the societal challenge of neurodegenerative diseases

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- **Frontotemporal dementia (FTD)** and **dementia with Lewy bodies (DLB)** show overlapping clinical symptoms with other types of dementia, especially in the early phases → accurate diagnosis is complicated
- **Disease-modifying therapies**, **specific biomarkers**, and **fundamental understanding of disease mechanisms** are lacking
- **Synaptic disturbances** have been suggested as the earliest pathological changes in neurodegenerative diseases
- SynaDeg postulates that **identification of early disease-specific synaptic alterations combined with measurable physiological disturbances** (*e.g.*, altered behaviour, autonomic, neurophysiological functions) can be used for **improved early diagnostics of FTD and DLB**
- ***Improved and earlier diagnostics → shorter diagnostic paths, better disease management, right treatments for right patients at the right time, better patient stratification in therapeutic trials***

SynaDeg project outcomes

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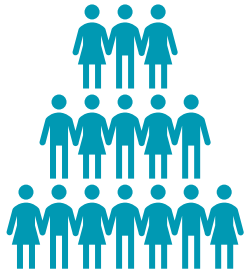

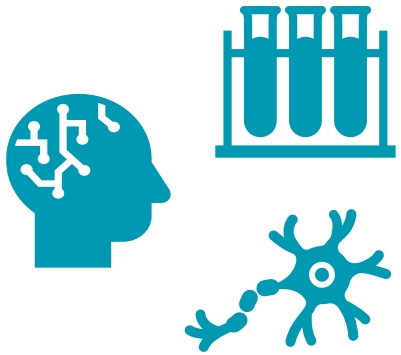

- ✓ **Well-characterized prospective cohort** with large amount of data focusing on **FTD** and **DLB** patients (AD patients as a neurodegenerative disease reference group)
- ✓ **Synaptic biomarkers** (neurophysiological and biofluid) for **early and differential diagnostics** of FTD and DLB correlating with physiological and other symptoms
- ✓ Improved understanding of **molecular-level mechanisms of synaptic dysfunction** in FTD and DLB → **new biomarker and therapeutic targets**
- ✓ Close collaboration with **patient organizations** for **improved dissemination and impact**

WP1 outcomes

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Correlation of disease symptoms with neurophysiological (TMS) changes

- ✓ **Logopenia** associates with changes in **SICI** (= short interval intracortical inhibition; *GABAergic*)
- ✓ Changes in **SAI** (= short-latency afferent inhibition; *cholinergic*) associate with **loss of insight** (unconsciousness of one's own state), **agitation**, and **aggression**

Autonomic symptoms in FTD and DLB

- ✓ Increased number of **autonomic symptoms**, incl. bowel and bladder-related symptoms and alterations of sexual functions, in FTD *vs.* AD patients
- ✓ The presence of autonomic symptoms does not remarkably differ between FTD and DLB patients
- ✓ More **sleep-associated symptoms** in FTD *vs.* DLB

➲ ***More accurate early diagnostics***

WP2 outcomes

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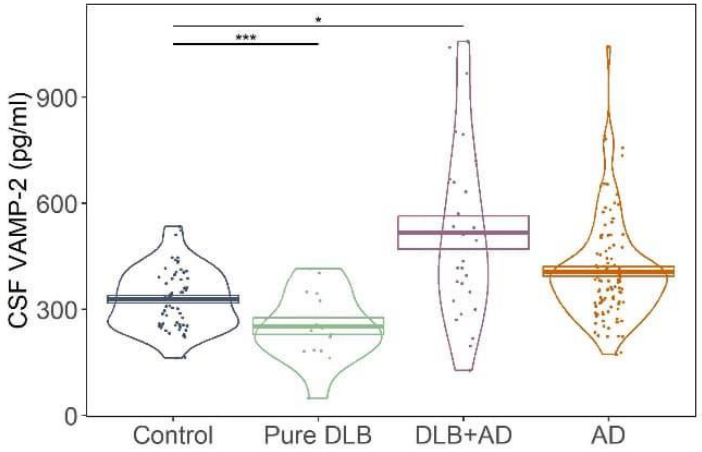
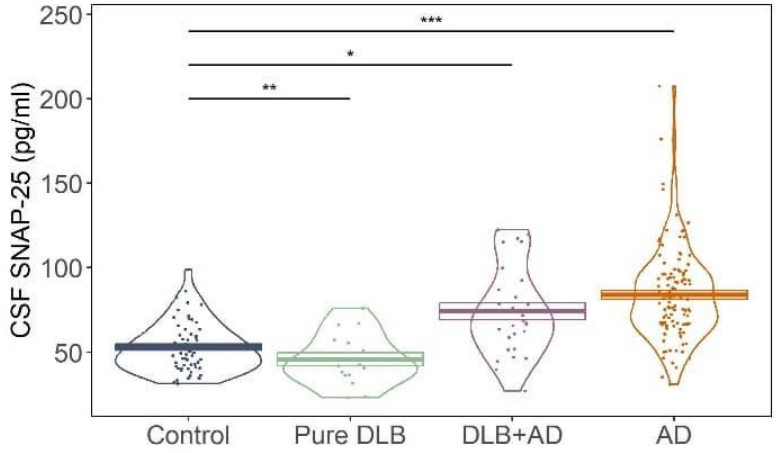
CSF levels of the synaptic SNARE complex proteins VAMP-2 and SNAP-25 are decreased in pure DLB *vs.* DLB+AD or AD





- ✓ **Worse phonemic fluency** was associated with lower CSF levels of VAMP-2 and SNAP-25 in patients with pure DLB but with elevated CSF levels of the synaptic proteins in DLB patients with AD comorbidity
- ✓ Promising results of the performance of the **blood-based assay of SNAP-25** in AD

➲ Aid identification of individuals who may benefit from therapeutic intervention and recruitment into DLB/AD clinical trials

WP3 outcomes

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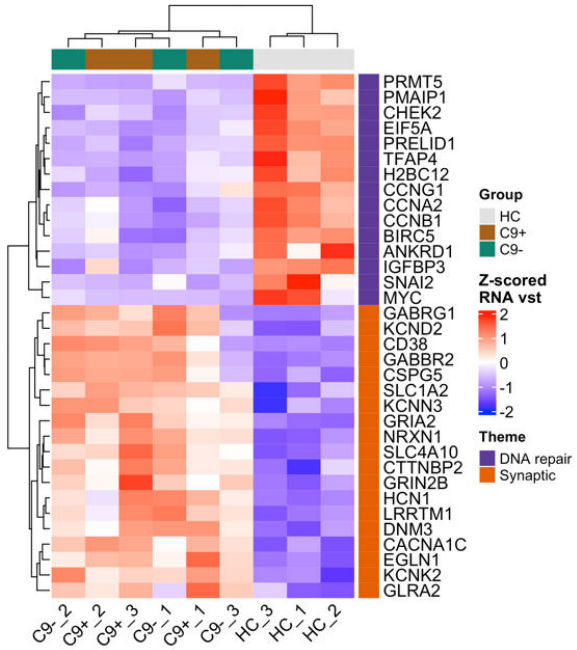
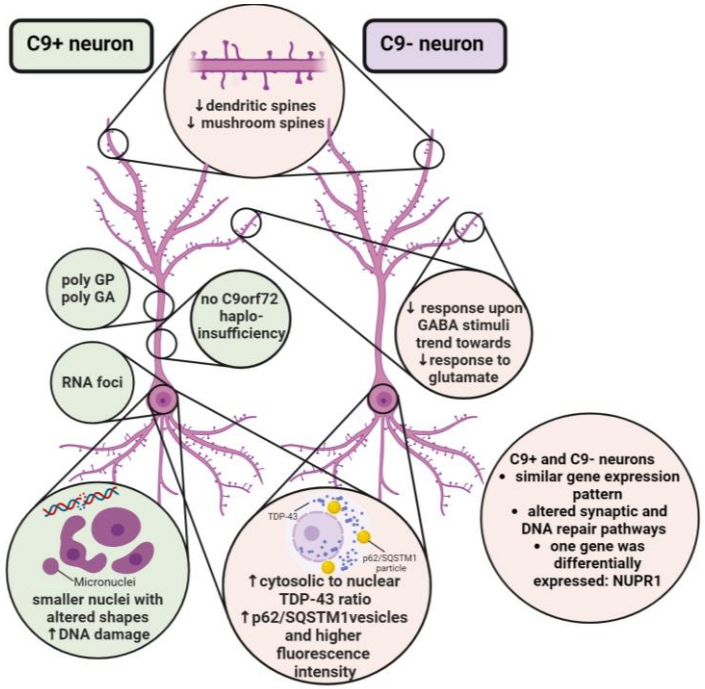
Sporadic (C9-) and *C9orf72* repeat expansion-carrying (C9+) FTD patient iPSC-neurons show FTD and C9+ associated pathologies and alterations in gene expression and synaptic function *vs.* controls (HC)





➲ ***Increased understanding of molecular disease mechanisms, new biomarker and mechanistic targets, and a platform for drug testing***

Successess and challenges

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- ☑ Well-working collaboration between partners
- ☑ Well-established previous expertise and infrastructures of the partners to support performing the tasks
- ☑ Participant recruitment more successful than expected (planned number exceeded)
- ☑ Set hypotheses of the project appear correct → data supporting the hypotheses have been achieved
- ☑ Clinically meaningful data achieved → healthcare/societal impact

- ⊖ Minor challenges due to some technical details in some specific tasks causing slight delays (but these have been overcome)
- ⊖ Fairly short duration and modest budget of the project

Lessons learned from working together across institutions

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- ☑ Good to have previous collaboration between at least some of the partners in the consortium (know your partners!)
- ☑ Regular consortium and WP meetings are needed
- ☑ Open joint discussions among partners and their research groups on the results and progress of the project are important
- ☑ Cross-institutional collaboration is needed to ensure the high scientific quality in the project (one partner/partner site cannot be an expert on everything)
- ☑ Excellent opportunities for international researcher exchange

Dissemination of project results

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- **Other researchers, industry representatives, health care professionals**:
  - Scientific publications (e.g., Huber et al., BioRxiv, 2024; Cervantes González et al., submitted manuscript)
  - Conferences, symposia (e.g., Kuopio Alzheimer Symposium 2022; AD/PD 2023; 33rd Alzheimer Europe Conference 2023, C9orf72 workshop 2024; ISFTD 2024)
  - Social media, press releases (partner and partner university web pages, X accounts, LinkedIn)
  - Research collaboration with experts in neuro-ethics and elderly law
- **Public, patient organizations**:
  - Social media, press releases (partner and partner university web pages, X accounts, LinkedIn)
  - PPI sessions in scientific conferences (Kuopio Alzheimer Symposium 2022)
  - Direct contacts with PO representatives, incl. SynaDeg Steering Committee meetings
  - Webinars in SynaDeg kick-off (2022; "*Recruiting FTD and DLB patients and ethicalness of research*") and closing (2025; "*Preventing structural and individual discrimination and stigmatization in EOD*") symposia
  - Yearly CIBERNET meetings (communication to public in native tongue)
  - Research materials delivered to patients (in native tongue)