

My vision: To advance knowledge on dementias and associated disorders, to improve diagnosis, treatment and care of patients in the context of geriatric psychiatry. To deliver state-of-the-art psychiatry and to be “a good doctor” with empathy and respect for my patients.

My research work is carried out mainly in collaboration. As a postdoc and for my habilitation thesis (1996), I did experimental work on brain energy metabolism, including the first description of brain insulin receptor deficits in AD, and helped to develop the “insulin hypothesis” of AD pathophysiology. Now, I am actively involved in neurocognitive, biochemical, neuroimaging and molecular genetic studies in Alzheimer’s disease and related disorders. Our research work requires a close link with the memory clinic (out-patient service) and a particular focus on biomarker-based diagnosis. This serves as the key point for biomaterial acquisition for our biobank (>1000 samples with deep phenotyping). I lead a small, quite productive group working on clinical services research and biomarkers. Innovative biomarker research is carried out in collaboration with small biotech companies (NOSELAB, HUMMINGBIRD). A particular focus of our group is on multicenter clinical trials supported by German governmental funding (BMBF, BMG, G-BA) (KORDIAL, REDALI-DEM, AD-COMBI, SIMAMCI, APA-AD, CBTlate, ENABLE), including large European translational projects supported by the European Union 5<sup>th</sup> – 7<sup>th</sup> Framework, the JPND and the Horizon2020 grant systems (ICTUS, DESCRIPA, EMIF, EADR, BIOMARK-APD, GERAD, RECAGE, EADB) and clinical drug trials sponsored by the pharmaceutical industry (Ph1b – Ph3).

Contribution to science: Since turn of the millennium, it is clear that translational research on Alzheimer’s disease and related dementias requires large international collaborative efforts with biobanking and deep phenotyping. The Alzheimer’s Disease Neuroimaging Initiative (ADNI) in the US has become the benchmark for these efforts. However, this lacks a focus on CSF biomarkers. To this means, we have contributed to national and international initiatives.

We are part of the central core of the German Competence Network on Dementias (DCN) (2002-2009, PI: Henn, ZI Mannheim / Maier, Bonn). Here, we built a cohort of >2000 patients in early stages of dementias with follow-up and established a biobank with neuropsychological and clinical data, neuroimaging and CSF; this biobank is still valid and used for analyses (Benson et al. 2022). Structurally, this network has resulted in a network of memory clinics which use the roughly the same assessment instruments and which have collaborated in several national joint multicenter clinical trials. Subsequent further efforts have led to the founding of the DZNE. The ZI, unfortunately, is not part of this important research hub. A recently founded educational society based on the DCN achievements is the German Network of Memory Clinics (DNG), where we lead two working groups. The DCN has established evidence (1) on the clinical relevance and confounding factors of the core CSF Alzheimer biomarkers for early diagnosis and prognosis (2) on the effects of a combination treatment of the current symptomatic drugs in mild-moderate AD dementia and its relative lack of effect in mild cognitive impairment. This evidence has been taken up into the current German Guideline recommendations.

A similar initiative was initiated 2002 on the European level: the European Alzheimer’s disease consortium (EADC) Here, I was among the founding executive board members

(initial PI: Winblad, Sweden, and Vellas, France), and I serve as Co-Chair since 2010. This is a network of academic expert memory clinics with clinical and research activities; the major aims are to conduct joint multicenter projects and to harmonize the modes of operation for diagnosis, treatment and care. Most of our European research projects have been carried out among centers of the EADC (see above). Mainly under the lead of Swedish and Dutch colleagues, we conducted several large multicenter projects on cultural determinants on the course of dementia (ICTUS), the relevance of CSF biomarkers (BIOMARK-APD), identified several new genetic risk factors and described a polygenic risk score (EADB), and explored several –omics analyses as diagnostic strategies (DESCRIPA, EMIF, EDAR). An Amyloid biomarker study group was formed from the three last mentioned projects to delineate the use and limitations of beta-amyloid determinations by PET and CSF, respectively as a core diagnostic biomarker for AD. Publication of the respective data sets is ongoing.

My latest extension of research activities has been to contribute to health services research, e.g. to an EU Horizon multicenter project investigating the effectiveness of a special care unit for behavioral disturbances in dementia, and to a BMBF-funded multicenter randomized controlled clinical on the effects of psychotherapy (CBT versus supportive therapy) in old-age depression. Results of these projects have not been published, yet.

My broader outreach: On the level of Heidelberg University, a Network on Aging Research (NAR) has been formed by Konrad Beyreuther as a PhD school, to which I contribute as a fellow. I am active in national and international guideline committees on dementias, and act as Co-Chair of the Mannheim faculty Ethics Committee. I co-founded 3 regional German Alzheimer Societies and serve on several Charity or funding organizations in the field of dementia. I contributed >60 textbook and handbook articles, supervised >20 doctoral dissertations and master theses and regularly give educational lectures to medical personnel and the general public on a regional, national and international level. Last but not least, I am a well-respected clinical psychiatrist with broad reputation in the field of dementia and old-age depression and I am active in treating patients (named by FOCUS Ärzteliste for many years).

#### Key output of the years 2020 – now

Contributing author to: the major international GWAS network in Alzheimer's disease (as part of the DCN-GERAD and EADB consortium, key paper: HAROLD et al. Nat Genet. 2009) and the world-wide largest consortium on the study of amyloid as a biomarker (DESCRIPA, EMIF, EADR, key paper: JANSEN et al. JAMA 2015)

Jansen IE, ... Frölich L, ... Hausner L, ... Ruiz A, Ramirez A, Cruchaga C, Lambert JC, van der Flier W. Genome-wide meta-analysis for Alzheimer's disease cerebrospinal fluid biomarkers. Acta Neuropathol. 2022 Sep 6. doi: 10.1007/s00401-022-02454-z. Epub ahead of print.

Jansen WJ, ... Frölich L, ... Hausner L, ... Zetterberg H. Prevalence Estimates of Amyloid Abnormality Across the Alzheimer Disease Clinical Spectrum. JAMA Neurol. 2022; 79(3):228-243.

de Rojas I, ... Frölich L, ... van der Flier WM, Ramirez A, Lambert JC, van der Lee SJ, Ruiz A. Common variants in Alzheimer's disease and risk stratification by polygenic risk scores. Nat Commun. 2021; 12(1):3417.

Contributing author to: major epidemiological meta-analysis of pre-dementia stages of Alzheimer's disease and consensus /guideline publications on dementias (leading role in EADC)

Gustavsson A, ... Frölich L, ... van der Flier WM. Global estimates on the number of persons across the Alzheimer's disease continuum. *Alzheimers Dement*. 2022 Jun 2. doi:10.1002/alz.12694. Epub ahead of print.

Boccardi M, ... Frölich L, ... Consortium for the Harmonization of Neuropsychological Assessment for Neurocognitive Disorders. Harmonizing neuropsychological assessment for mild neurocognitive disorders in Europe. *Alzheimers Dement*. 2022; 18(1):29-42.

Frederiksen KS, ... Frölich L, ... Waldemar G. A European Academy of Neurology guideline on medical management issues in dementia. *Eur J Neurol*. 2020; 27(10):1805-1820.

Primary or senior author on work from our own group with PhD student/Co-worker as first author

Benson GS, Bauer C, Hausner L, ... Frölich L. Don't forget about tau: the effects of ApoE4 genotype on Alzheimer's disease cerebrospinal fluid biomarkers in subjects with mild cognitive impairment-data from the Dementia Competence Network. *J Neural Transm*. 2022; 129(5-6):477-486.

Celik S, ... Frölich L, Teichmann B. Cross-cultural comparison of MMSE and RUDAS in German and Turkish patients with Alzheimer's disease. *Neuropsychology*. 2022; 36(3):195-205.

Frölich L, ... Quality of Life and Caregiver Burden of Alzheimer's Disease Among Community Dwelling Patients in Europe: Variation by Disease Severity and Progression. *J Alzheimers Dis Rep*. 2021; 5(1):791-804.

Contributing author to: the largest RCT world-wide on a pharmacological agent against apathy in Alzheimer's disease; German network study

Maier F, ... Frölich L, Hausner L, ... Jessen F. Bupropion for the Treatment of Apathy in Alzheimer Disease: A Randomized Clinical Trial. *JAMA Netw Open*. 2020; 3(5):e206027.