Annakaisa Haapasalo (ed.)

6th Kuopio Alzheimer Symposium

On the road to early diagnosis, treatment, and prevention of Alzheimer's disease
Kuopio, Finland, June 14-16, 2012

Program and Abstracts

Publications of the University of Eastern Finland
Reports and Studies in Health Sciences

UNIVERSITY OF
EASTERN FINLAND

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Welcome to 6th Kuopio Alzheimer Symposium

Dear Friends and Colleagues,

It is my great pleasure to welcome you to the 6th Kuopio Alzheimer Symposium held in Kuopio, Finland, from 14 to 16 June, 2012, and organized by University of Eastern Finland, Institute of Clinical Medicine, Neurology, The Finnish Alzheimer's Disease Research Society, AlzPoint, and The Doctoral Program in Molecular Medicine.

Alzheimer's disease (AD) is one of the most important health challenges worldwide. AD is recognized as a research priority in Europe. In Finland, the National Memory Program was recently published. This year's Kuopio Alzheimer Symposium brings together the current leaders involved in clinical and basic research and provides a forum for new ideas for future research and subsequently for treatment and prevention options. The Finnish program of the Memory Day, "Muistipäivä" focuses on the guidelines of good care. The First Kuopio Alzheimer Symposium was held in January of 1999 in freezing temperatures. This time we decided to fulfill the wish of many of you to organize the meeting in the summer to provide you also an opportunity to experience the Finnish summer and the midnight sun.

We are proud to present our exciting program, which will focus on new results concerning early diagnosis, new advances in brain imaging, biomarkers for AD, search for drug targets, prevention, and treatment and care.

I warmly welcome you all to enjoy this inspirational scientific event!

Kuopio, May 15, 2012

Hilkka Soininen, MD, Ph.D.
Professor
Chair of the Organizing Committee

6TH KUOPIO ALZHEIMER SYMPOSIM

Organized by

University of Eastern Finland, Institute of Clinical Medicine – Neurology
The Finnish Alzheimer's Disease Research Society
AlzPoint
The Doctoral Program in Molecular Medicine

International Scientific Organizing Committee

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Juha Rinne, University of Turku, Turku, Finland
Bengt Winblad, Karolinska Institutet, Stockholm, Sweden

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6th Kuopio Alzheimer Symposium

Program and Abstracts

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6th Kuopio Alzheimer Symposium

PROGRAM

Thursday, June 14
Memory Day - Finnish Session / Muistipäivä

The Finnish Session - Memory Day - program is targeted for nurses, doctors, psychologists and other personnel working with memory patients.
Muistipäivän ohjelma on suunnattu erityisesti perusterveydenhuollossa, kotihoidossa ja hoitokodeissa muistipotilaiden kanssa työskentelevälle hoitohenkilöstölle, psykologeille ja lääkäreille.

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Teemu Paajanen, Itä-Suomen yliopisto, Kuopio

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Anne Airaksinen, Kuopion yliopistollinen sairaala, Kuopio

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6th Kuopio Alzheimer Symposium

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Thursday, June 14
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Päivi Voutilainen, Ministerial Counselor, Social Affairs, Ministry of Social Affairs and Health
Hilkka Soininen, Chair of the Organizing Committee

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Bengt Winblad, Karolinska Institutet, Stockholm, Sweden
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Robert Vassar, Northwestern University, Chicago, IL, USA

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Matej Orešič, VTT Technical Research Centre of Finland, Helsinki, Finland

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Chairs

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Saturday, June 16
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Janne Martikainen, University of Eastern Finland, Kuopio, Finland

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Hilkka Soininen, Chair of the Organizing Committee, University of Eastern Finland

Abstracts for invited talks

Thursday, June 14

Opening symposium

Keynote Lecture

CAN WE FIND DISEASE-MODIFYING TREATMENTS FOR ALZHEIMER'S DISEASE?

Bengt Winblad
Karolinska Institutet, Stockholm, Sweden

Alzheimer's disease (AD) is the most common cause of dementia in advanced age. Currently, available medications improve AD symptoms and development of disease-modifying drugs is a very active area of research, which includes cholinergic, anti-amyloid compounds, drugs targeting tau-protein or mitochondria, neurotrophins and other therapeutic approaches.

The amyloid cascade hypothesis dominates current disease modifying drug development strategies, but the exact role of Aβ in the AD pathogenesis is yet unclear, and so is the therapeutic role of Aβ removal.

Identification of effective disease-modifying drugs will benefit from understanding the interplay between mechanisms causing neurodegeneration in AD. Combined therapy could be a more effective strategy to halt AD progression. Solving methodological problems in clinical trials on AD - including use of standardized diagnostic criteria able to identify homogeneous group of patients, appropriate treatment duration and measures of disease-modifying effects - will help finding a cure for AD.

The lecture will summarize current treatment possibilities for AD and give an overview of the main findings of new therapeutics in AD, focusing mainly on compounds in the human testing phase that will have disease-modifying effect.

Keynote Lecture

BACE1, THE ALZHEIMER'S β-SECRETASE ENZYME, IN HEALTH AND DISEASE

Robert Vassar
Department of Cell and Molecular Biology, Feinberg School of Medicine, Northwestern University, Chicago, IL, USA

The β-amyloid (Aβ) peptide is the major constituent of amyloid plaques in Alzheimer's disease (AD) brain and is likely to play a central role in the pathogenesis of this devastating neurodegenerative disorder. The β-secretase, β-site amyloid precursor protein cleaving enzyme 1 (BACE1; also called Asp2, memapsin 2), is the enzyme responsible for initiating the generation of Aβ. Thus, BACE1 is a prime drug target for the therapeutic inhibition of Aβ production for the treatment or prevention of AD. Since its discovery over 10 years ago, much has been learned about BACE1.

This seminar will describe BACE1 properties, physiological functions, and dysregulation in AD. The therapeutic potential of BACE1 inhibitors for AD will also be considered. Particular focus will be placed upon our novel results demonstrating a role of BACE1 in the axon guidance of olfactory sensory neuron axons to specific odorant receptor glomeruli in the olfactory bulb and the therapeutic implications of these findings.

Friday, June 15
Main symposium

I Early diagnosis

PROGRESS OF DIAGNOSTIC GUIDELINES OF AD

Gunhild Waldemar
Copenhagen University Hospital, Denmark

WHAT HAVE WE LEARNED FROM MCI STUDIES?

Pieter Jelle Visser[1,2]
[1]*Department of Psychiatry and Neuropsychology, Institute of Mental Health and Neuroscience (MeHNS), University of Maastricht, Maastricht, Netherlands,* [2]*Department of Neurology, Alzheimer Centre, VU Medical Centre, Amsterdam, Netherlands*

The concept of Mild Cognitive Impairment (MCI) was introduced 20 years ago. It was considered a prodromal stage of Alzheimer's disease (AD). However, it has become clear that MCI is a heterogeneous condition and that only a subset of subjects with MCI will progress to Alzheimer-type dementia.

In the presentation, I will discuss the course of MCI, predictors of outcome, and opportunities for treatment. I will also discuss the use of biomarkers for the diagnosis of MCI-due-to-AD. Using the amyloid cascade as a model for the development of AD, I will demonstrate that the diagnostic accuracy of these biomarkers is dependent on their position in the amyloid cascade. Markers that measure processes upstream in the amyloid cascade are useful for early diagnosis, while markers for processes downstream in the cascade are useful for prognosis.

COMPUTER-ASSISTED EARLY DIAGNOSIS OF ALZHEIMER'S DISEASE

Jussi Mattila[1], Hilkka Soininen[2,3], Gunhild Waldemar[4], Anja Simonsen[4], Hilkka Runtti[1], Jyrki Lötjönen[1]

[1]VTT Technical Research Centre of Finland, Tampere, Finland, [2]Institute of Clinical Medicine, Neurology, University of Eastern Finland, Kuopio, [3]Department of Neurology, Kuopio University Hospital, Kuopio, Finland, [4]Memory Disorders Research Group, Department of Neurology, University Hospital Rigshospitalet, Copenhagen

Rationale: Reaching a diagnosis of Alzheimer's disease (AD) is a complex and partly subjective process. A clinical decision support system that evaluates a patient's disease state in an objective and evidence-based manner could improve consistency and accuracy of diagnostics. A tool providing an estimate of a patient's disease state could also help to monitor disease progression and to make the diagnosis earlier.

Methods: Disease state fingerprint (DSF) is a method that was developed for detecting early AD and for monitoring disease progression. Its performance was evaluated in comparison to several state-of-the-art classification methods. The method was then implemented within a clinically viable software tool, which was tested with clinicians using a retrospective cohort. Subsequent studies regarding longitudinal monitoring of disease progression and identification of early AD cases were done to learn more about the properties and potential of the DSF method.

Results: Using the DSF for predicting AD in mild cognitive impairment (MCI) subjects reaches accuracy similar to state-of-the-art classifiers. A clinical tool with the DSF implementation allowed clinicians to have more confidence in their diagnoses and also reach better accuracy than by having the data on paper charts. Longitudinal monitoring of patients using the DSF method was shown to be feasible and revealed potential early AD cases in an MCI cohort. The concept of evidence-based disease state was also shown to identify groups of MCI subjects with decisive evidence of early AD in their measurement data.

Conclusion: The DSF is an evidence-based method for analyzing patient data to support diagnostics of AD. It was designed to be accurate, but also to be easily applied and interpreted in clinical practice. It has been shown to work with various data and improve clinicians' ability to read heterogeneous patient measurements. It also has convenient properties that allow monitoring of disease progression and identification of patients with strong evidence of early AD.

BRAIN BIOPSY - WINDOW TO EARLY PATHOGENESIS

Ville Leinonen
Neurosurgery of NeuroCenter, Kuopio University Hospital and Institute of Clinical Medicine, University of Eastern Finland

Amyloid-β (Aβ) plaques, along with intracellular neurofibrillary tangles largely comprising hyperphosphorylated tau (HPτ), are considered the hallmarks of Alzheimer's disease (AD). Aβ accumulation in brain tissue can be seen years before clinical manifestation of AD, thus offering a window for even preclinical diagnosis. Brain biopsies are seldom used in the diagnosis of AD but brain surgery for the diagnostic evaluation and treatment of normal pressure hydrocephalus (NPH) – a potentially treatable cause of dementia – enable to obtain small brain tissue samples without adding risk for the patient. In addition, AD-related brain pathologies are frequently seen in the NPH patients and AD is the most frequent differential diagnosis of NPH.

Kuopio Neurosurgery NPH Registry and Tissue Bank (www.uef.fi/nph) contain small cortical brain biopsies from over 650 patients with suspected or diagnosed NPH. We have demonstrated the predictive value of brain biopsy for the clinical diagnosis of AD. The presence of both Aβ and HPτ indicated later diagnosis of AD with a high specificity (98%) but with a rather low sensitivity (36%). Aβ alone was sensitive (87%) for AD but less specific (69%). The absence of both Aβ and HPτ nearly excluded the later appearance of AD. Furthermore, the presence of Aβ and HPτ in the biopsy correlated with CSF Aβ and tau levels.

Brain biopsies - when available – are a useful diagnostic tool of AD, can validate less invasive biomarkers, and may help to identify novel markers for AD.

HOW EARLY AD STARTS?

Irina Alafuzoff[1,2]
[1]*Department of Immunology, Genetics and Pathology, Uppsala University, Uppsala, SE-75185, Sweden,* [2]*Department of Clinical Pathology and Cytology, Laboratory Medicine, Uppsala University Hospital, Uppsala, SE-75185, Sweden*

In subjects with Alzheimer's Disease (AD), aggregates of hyperphosphorylated tau (HPtau) are seen in the brain. HPtau display a predictable regional distribution, indicating a stepwise, time-dependent, orderly progression of HPtau pathology. It is noteworthy that HPtau is seen contrary to what was suspected already at an early age. In a transgenic mouse model, it has been shown that HPtau pathology can be transmitted and spreads to neighboring brain regions. Based on this observation the question was raised: are most neurodegenerative disorders with abnormal protein aggregations similar to prion disorders, that is, is the spread of the disease reminiscent of those by which prions spread? In sum, should tauopathy commonly observed in aged brains be considered transmissible and prone to spread after initiation? The finding that most of us display some extent of tau pathology with advanced age, and the suggestion that protein alterations spread in a predicted way are worth a serious concern.

AUTOMATIC ANALYSIS OF MRI – EXPERIENCE FROM AddNeuroMed STUDY

Andy Simmons
Kings College, London, UK

There is an urgent need for Alzheimer's disease (AD) biomarkers, especially in the context of clinical trials. Biomarkers for early diagnosis, disease progression, and prediction are most critical, and disease-modification therapy development may depend on the discovery and validation of such markers. AddNeuroMed is a cross European, public/private consortium developed for AD biomarker discovery funded by the European Union and EFPIA (1). AddNeuroMed has focused on the use of automated Magnetic Resonance Imaging measures as biomarkers in their own right and additionally as a tool for the discovery and validation of blood based biomarkers.

I will outline the development and design of AddNeuroMed and report results from the AddNeuroMed study covering both the use of Magnetic Resonance Imaging (2) and progress towards the development of plasma and other blood based biomarkers by using automated MRI measures (1). Despite the obstacles to such markers, we have identified a range of markers which have been independently replicated and show the potential for such approaches. AddNeuroMed has illustrated the benefits of combining multiple markers for classifying Alzheimer's disease and healthy controls, as well as predicting conversion from Mild Cognitive Impairment to Alzheimer's Disease.

References:

1. Lovestone S, Francis P, Strandgaard K. Biomarkers for disease modification trials - the innovative medicines initiative and AddNeuroMed, J Nutr Health Aging, 2007, 11(4), 359-361
2. Simmons A, Westman E, Muelboeck S *et al*. MRI measures of Alzheimer's disease and the AddNeuroMed study, Annals NYAS, 1180, 47-55, 2009

MULTIMODAL ANALYSIS OF MRI IN EARLY DIAGNOSIS AND FOLLOW-UP OF AD

Lars-Olof Wahlund
Karolinska Institutet, Stockholm, Sweden

Alzheimer's disease (AD) has probably a heterogeneous origin. Even if Aβ is a key player in the pathophysiology, several other mechanisms are of importance for the development the disease.

In order to diagnose AD early and accurately, measurement of several disease-related parameters are needed. One example is to simultaneously analyze several other brain areas apart from structures in the medial temporal lobe. MR technique makes it possible to study not only morphometrics but also brain metabolites using magnetic resonance spectroscopy, the integrity of the white matter with diffusion tensor imaging and the thickness of the cortex.

We have in several cohorts of AD and MCI patients and controls studied brain morphometry and brain function and elucidated the diagnostic value of these parameters by combining different volume measures, brain metabolites, cortical thickness and white matter parameters with an added value design. The purpose was to see if we could detect a pattern of changes specific for AD that was already present in MCI subjects. We also aimed to investigate if the diagnostic accuracy was increased if the imaging markers were used together with other markers from e.g. CSF or blood.

HIPPOCAMPAL VOLUMETRY AND MORPHOMETRY – RESULTS FROM ADNI COHORT

Jyrki Lötjönen[1], Robin Wolz[2], Valtteri Julkunen[3,4], Juha Koikkalainen[1], Eini Niskanen[3,4], Dong Ping Zhang[2], Lennart Thurfjell[5], Daniel Rueckert[2], Gunhild Waldemar[6], Hilkka Soininen[3,4]

[1]VTT Technical Research Centre of Finland, Tampere, Finland, [2]Imperial College London, London, UK, [3]Institute of Clinical Medicine, Neurology, University of Eastern Finland, Kuopio, [4]Department of Neurology, Kuopio University Hospital, Kuopio, Finland, [5]GE Healthcare Ltd, Uppsala, Sweden, [6]Memory Disorders Research Group, Department of Neurology, University Hospital Rigshospitalet, Copenhagen

Rationale: The role of structural brain magnetic resonance imaging (MRI) is becoming more and more emphasized in the early diagnostics of Alzheimer's disease (AD). Hippocampal area is one of the first areas affected by the disease. Efficient automated tools for analyzing the hippocampal area from MRI images are needed.
Methods: Several methods can be used to characterize changes in the hippocampal area, such as methods computing hippocampus volume, atrophy-rate, cortical thickness, and tensor-based morphometry and manifold learning-based techniques. In this work, we compare the performance of these different methods in diagnostics of AD using imaging data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort. The data were divided into four groups: healthy controls, stable mild-cognitive impairment (SMCI) cases who did not convert to AD during a follow-up period, progressive MCI cases (PMCI) who converted to AD during a follow-up period, and AD cases.
Results: The results show that tensor-based morphometry produced the overall best results but there is no big difference between the methods. The classification accuracy between healthy controls and AD patients was between 81-89 %. The corresponding numbers between healthy controls and PMCI cases and between SMCI and PMCI cases were 77-79 % and 56-65 %, respectively. Combining all features improved the results in all study experiments.
Conclusion: Several methods can be used in characterizing the changes due to AD. The methods produce comprehensive information and the best results are obtained when combining results from different methods. Because all these methods are fully automatic, the use of multiple methods does not pose other constraints to their use as the increased computation time.

MRI IN MEMORY DISORDERS – CLINICAL EXPERIENCE

Ritva Vanninen
University of Eastern Finland, Kuopio, Finland

OPTIONS OF PET IN MEMORY DISORDERS

Juha O. Rinne
Turku PET Centre, University of Turku and Turku University Hospital, Turku, Finland

Positron emission tomography (PET) is a versatile and functional imaging method to study brain functions in living humans. In memory disorders, PET can be used in the early diagnosis, differential diagnosis, follow-up, development of treatments and evaluation of treatment effects.

Different memory disorders cause typical pattern of glucose hypometabolism which can be studied with fluorodeoxyglucose (FDG) PET. In Alzheimer´s disease (AD), temporo-parietal hypometabolism is seen. In frontotemporal dementia, impaired metabolism is located in the frontal lobes and in the anterior temporal lobes. In distinction from AD, occipital hypometabolism is seen in patients with dementia with Lewy bodies (DLB).

Investigating brain neurotransmitter systems give more specificity. These investigations are still mainly at research stage. However, dopamine transporter imaging seems to be also clinically helpful in distinguishing between AD and DLB.

Imaging of pathological protein aggregations (e.g. β-amyloid plaques or tau protein) or neuroinflammation (activated microglia or astrocytosis) give the opportunity for "pathology-specific" imaging. Amyloid imaging is sensitive to separate patients with AD from healthy volunteers. In addition, positive amyloid imaging in patients with mild cognitive impairment (MCI) strongly predicts conversion to AD later. Some healthy elderly individuals are positive in amyloid imaging. Clinical follow-up of these individuals is very important to evaluate the role of amyloid imaging to reveal and predict early AD. [18F]FDDNP binds also to neurofibrillary tangles and there are also other PET ligands that show promise in imaging tau pathology. Neuroinflammation may coexist or even precede degenerative changes in memory disorders.

PET imaging can be used also to help in the development of AD therapies or to evaluate their effects, as shown earlier with blood flow, glucose metabolism and cholinergic system imaging, and more recently also with amyloid imaging.

In the future, multitracer or multimodality imaging could help to understand the complex pathophysiology of AD and other memory disorders and to aid in developing more sensitive and specific diagnostic methods and therapies.

MR IMAGING OF AMYLOID PLAQUES, HEMODYNAMIC AND METABOLIC CHANGES – EXPERIENCE FROM EXPERIMENTAL MODELS OF ALZHEIMER'S DISEASE

Olli Gröhn
Department of Neurobiology, A.I.Virtanen Insititute, University of Eastern Finland

MRI provides a versatile toolbox of non-invasive imaging approaches which can be used to assess structural, functional and metabolic changes in animal models of Alzheimer's disease.

Recent advances in MRI techniques has made possible to detect individual amyloid plaques in the brain of AD transgenic mouse *in vivo*, and follow their growth over time (1). With the current approaches, the native contrast of MRI plaques is mostly based on presence of iron in the plaques. Therefore, the contrast obtained may vary between different animal models and is not necessarily specific to amyloid plaques. Thus, there is need and ongoing efforts to develop contrast-enhancing agents to increase the specificity and sensitivity in amyloid plaque MRI. As amyloid reduction has been for years a major therapeutic objective, this kind combination of animal model and specific non-invasive imaging is expected to be extremely valuable in development of treatment.

MRI can be used to detect hemodynamic changes either using MRI contrast agents or completely non-invasively using so called arterial spin-labeling approach, which is becoming increasingly popular (2). It is not fully established if decreased blood flow in AD is a cause or consequence of the disease. Nonetheless, hypoperfusion in AD is associated with both structural and functional changes in the brain and offers a promising putative biomarker that could potentially identify AD in its pre-clinical state and be used to explore treatments to modify the progression of the disease.

^{1}H Magnetic resonance spectroscopy (MRS) can be used to obtain metabolic profile consisting of up to ~20 metabolites, each potentially providing information about unique *in vivo* pathological processes at the molecular or cellular level. Reduction in the levels of N-acetylaspartate and glutamate has been found in APP-PS1 mice with advancing age. Interestingly, these results agree with results obtained from *in vivo* human MRS studies, emphasizing the translational nature of information obtainable with MR techniques.

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NEW OPTIONS FOR BIOMARKERS OF MEMORY DISORDERS

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Cerebrospinal fluid biomarkers may be used to monitor disease processes in the brain. Applications are available for research and clinical management for several neurological diseases, including Alzheimer's disease (AD), with usages including diagnosis, prognosis and patient stratification. Within dementia research, major efforts are devoted to the discovery and validation of biomarkers for early diagnosis of AD. This is largely motivated by the ongoing development of disease-modifying AD drugs. The most promising CSF biomarkers for early diagnosis of AD are decreased levels of β-amyloid42, reflecting amyloid plaque pathology, increased levels of total-tau, reflecting axonal degeneration, and increased levels of abnormally phosphorylated tau, reflecting tangle pathology. Most AD patients have this CSF biomarker pattern already at early stage, before onset of clinical dementia. There is now some evidence of CSF biomarker alterations also in preclinical stages and of time-dependent differences in the pathological development of the biomarkers. However, multi-center investigations have found considerable between-center variation in CSF biomarker levels. This is an obstacle towards broad implementation of these measurements. Therefore, a global quality control program was started by The Alzheimer's Association, which now includes more than 80 laboratories world-wide. The program may aid in harmonization of CSF biomarkers for early AD diagnosis. Other initiatives have also been started to standardize measurements. Finally, CSF biomarkers are being developed to monitor treatment effect and toxicity of novel AD drugs.

CAN WE FIND BLOOD MARKERS FOR AD?

Markus Otto
University of Ulm, Germany

METABOLOMICS AND LIPIDOMICS IN ALZHEIMER'S DISEASE

Tuulia Hyötyläinen[1], Marko Sysi-Aho[1], Sanna-Kaisa Herukka[2], Ismo Mattila[1], Minna Hartonen[1], Jyrki Lötjönen[1], Hilkka Soininen[2], Matej Orešič[1]
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Mild cognitive impairment (MCI) is considered as a transition phase between normal aging and Alzheimer's disease (AD). MCI confers an increased risk of developing AD, although the state is heterogeneous with several possible outcomes including even improvement back to normal cognition. Ideally, the AD biomarkers (1) would reflect the disease related biological processes and (2) may be measured noninvasively, such as a blood test. Metabolomics, a discipline dedicated to the global study of small molecules (i.e., metabolites) in cells, tissues and biofluids, has emerged as a powerful tool for characterization of complex phenotypes affected by both genetic and environmental factors.

We sought to determine the serum metabolic profiles associated with progression to and diagnosis of Alzheimer's disease in a well-characterized prospective study. At the baseline assessment, the subjects enrolled in the study were classified into three diagnostic groups: healthy controls (n=46), MCI (n=143), and AD (n=47). Among the MCI subjects, 52 progressed to AD in the follow-up. Global metabolomics approach using two platforms with broad analytical coverage, from molecular lipids (UPLC-MS) to small polar metabolites (GC×GC-TOFMS), was applied to analyze baseline serum samples from subjects involved in the study and to associate the metabolite profiles with the diagnosis at baseline and in the follow-up [1].

At baseline, AD patients were characterized by diminished phospholipids, including ether phospholipids, phosphatidylcholines, sphingomyelins and sterols. Concentration of serum histamine was elevated in AD patients. A three-metabolite biomarker signature was identified which was predictive of progression to AD in the follow-up [1]. The major contributor to the predictive model was a major cerebrospinal fluid (CSF) metabolite 2,4-dihydroxybutanoic acid (2,4-DHBA), which was upregulated in AD progressors ($P=0.0048$), indicating potential involvement of hypoxia in the early AD pathogenesis. This was supported by the pathway analysis of GC×GC-TOFMS data using MPEA [2] which identified upregulation of pentose phosphate pathway in patients who later progressed to AD.

The GCxGC-TOFMS platform was also applied to analyze the CSF samples, from a subset of patients included in serum metabolomics study. We compared two groups: (1) Control group - controls and stable MCI combined (N=26), and (2) AD group - AD and progressive MCI (n=40). Our study confirmed that some of the metabolites associated with AD as measured in blood are also present in CSF. Furthermore, 2,4-DHBA was found significantly upregulated in the AD group ($P<0.05$), indicating that elevated serum levels of this metabolite may reflect changes of 2,4-DHBA metabolism in the brain.

Established CSF markers of AD, β-amyloid$_{1-42}$ (Aβ42), total tau protein (T-tau), and tau phosphorylated at position threonine 181 (P-tau), were also measured. Among these, only Aβ42 was significantly downregulated in the AD group ($P<0.05$). However, CSF profiles of Aβ42 and 2,4-DHBA were not correlated. Both biomarkers produced similar diagnostic models when applied alone, but the model was significantly improved (AUC=0.80) when Aβ42 and 2,4-DHBA were combined.

Together, our findings primarily implicate the roles of brain hypoxia, oxidative stress as well as membrane lipid remodeling in AD. The independence of 2,4-DHBA and Aβ42 in CSF suggests that dysregulation of 2,4-DHBA in patients who later progress to AD may reflect a novel pathway in AD pathogenesis. Establishment of pathogenic

relevance of predictive biomarkers such as ours may not only facilitate early diagnosis but may also help identify new therapeutic avenues.

Acknowledgements:
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SEARCHING RISK GENES FOR AD – EXPERIENCES FROM THE INTERNATIONAL INITIATIVES

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Over a 16-year period (from 1993 to 2009), only the apolipoprotein E (*APOE*) gene was found to be a major risk factor for AD. Beyond *APOE* and despite strong research efforts (i.e. more than 660 suggested candidate genes for AD), there was until recently an absence of consensus on the genetic determinants of AD. This frustrating observation was mainly driven by major methodological issues. However, as for other multifactorial diseases, the study of AD genetics benefited from the use of very high-throughput genotyping analyses. These approaches (so called, genome wide association study, GWAS) involve hundreds of thousands (or even millions) of genetic polymorphisms and case-control studies including thousands of individuals (with the need for large consortium setting-ups).

Within this rapidly changing technical, methodological and collaborative context, the general picture of AD genetics has been already massively modified with the report of 10 new genetic determinants of AD and the exclusion of a large proportion of older promising genes. A more exhaustive knowledge of the AD genetic structure is now expected to be released in the next few months with the completion of the International Genomics of Alzheimer's Project. This project groups together the main four consortiums working on GWAS and will finally include 30,043 AD cases and 48,980 controls. This will probably again lead to the discovery of unexpected genes.

Saturday, June 16
Main symposium

IV Search for drug targets

FUNCTIONAL GENETICS – APPROACH TO DRUG TARGETS

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Alzheimer's disease (AD) is the most common neurodegenerative disorder in the world, which affects up to 50% of individuals above the age of 85. As the aging population continues to increase globally, treatment of AD and other age-associated neurodegenerative diseases is becoming increasingly important, not only from a human point of view, but also from an economic perspective. In recent years, several attempts have been made to find novel susceptibility genes for AD. Particularly genome-wide association (GWA) and meta-analysis-based studies have identified several risk variants in different genes, which significantly associate with AD in different ethnic populations. Consequently, it is estimated that these already identified risk gene variations together with the established causative mutations in *APP* and *presenilin* genes account for approximately 50% of the observed heritable aggregation of the disease. This indicates that additional susceptibility still genes still exist. Finding these novel risk genes and their subsequent functional characterization are extremely important tasks as these efforts may pave the way for the development of new biomarkers in the future. More specifically, it is likely that these new surrogate markers will be applied for risk, disease progression, and early diagnosis assessments. It is also expected that the functional genetics approach will identify specific new molecular targets in AD pathogenesis underlying its clinical manifestations. This again may allow the development of novel intervention approaches to slow down or even halt the progression of AD.

PROTEOMICS FOR ALZHEIMER'S DISEASE - SECRETASES AS THERAPEUTIC TARGETS

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Rationale: β-secretase (BACE1) is a major drug target in Alzheimer's disease. Possible side-effects of chronic BACE1 inhibition in patients are largely unknown, but may stem from the poorly understood physiological function of BACE1. In fact, several new phenotypes in brain and pancreas of BACE1-deficient mice were reported recently, but the substrates responsible for the phenotypes are largely unknown.
Methods: We developed a novel proteomic workflow based on quantitative mass spectrometry and determined BACE1 substrates in neurons and mouse brain on a proteome-wide scale.
Results: We identified the secretome of primary murine neurons, which may be used for biomarker studies. Additionally, we identified – besides APP and its homologs – over 20, mostly novel, physiological substrates of BACE1 and validated several of them in BACE1-deficient neurons and mice.
Conclusion: The new substrates point to a central function of BACE1 in neurite outgrowth and synapse formation. The identification of novel BACE1 substrates is not only the basis for a better understanding of BACE1 function and of the phenotypes in BACE1 knock-out mice, but will also allow to better evaluate the therapeutic potential of BACE1 and to develop biomarkers for monitoring potential side-effects of BACE1 inhibition in clinical trials of Alzheimer's disease.

IS THERE A LINK BETWEEN AD AND EPILEPSY?

Asla Pitkänen
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For a long time, patients with Alzheimer's disease (AD) have been known to have myoclonic seizures. Recently, it was shown that the risk of unprovoked partial or generalized seizures is up to 86-fold in patients with early onset of AD. Moreover, it was hypothesized that daily cognitive fluctuations in AD could relate to the occurrence of undiagnosed complex partial seizures. Many different mouse strains overexpressing amyloid precursor protein (APP) show spontaneous seizures and have interictal epileptiform discharges. The question is: what triggers multiple seizure types or hyperexcitability in AD? Recent data suggest that processing products of APP can modulate several ion channels. Further, enzymes contributing to APP processing may use Na-channel subunits as substrates, and consequently, affect Na-channel trafficking and composition in cell membranes leading to hyperexcitability. New data demonstrate an association between tau hyperphosphorylation and epileptogenesis. Moreover, reduction of tau has an antiepileptic effect.

The presentation will give an update of the possible role of amyloidogenesis and tau in epileptogenesis and ictogenesis.

USE IT OR LOSE IT: ADULT NEUROGENESIS AND LEARNING

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New neurons are generated every day in the adult mammalian hippocampus. The rate of adult neurogenesis depends on a variety of factors ranging from age to stress to alcohol consumption. To put it simple, generally healthy factors like aerobic exercise promote neurogenesis whereas unhealthy factors, such as sleep loss, suppress it. However, no matter how many cells are initially produced, most of the cells will die shortly after their generation. This is unless one engages in some kind of effortful learning during a specific time window when the cells are immature. If learning does occur, the new cells are more likely to survive and mature into fully functional neurons. In addition to learning promoting neuronal survival, some types of learning depend on the presence of adult-born new neurons. These functions include for example associating temporally non-overlapping events as well as learning to distinguish between locations that reside close to each other. Overall, promoting adult neurogenesis improves, while disrupting neurogenesis impairs, performance on these complex tasks. To summarize, neurogenesis and learning together maintain a fit and adaptive brain throughout life.

Disruptions in adult neurogenesis are evident in mouse models of Alzheimer's disease (AD) often before other markers, such as neuronal loss or amyloid deposition, can be detected. Consequently, hippocampal adult neurogenesis might be a potential target for treatments aimed to prevent or alleviate the symptoms of AD. However, research on the topic is still rather sparse and results inconclusive.

THE PLEIOTROPIC MECHANISM OF THE OMEGA-3 FATTY ACID DHA, CHOLESTEROL, GANGLIOSIDES AND OTHER DIETARY LIPIDS ON ALZHEIMER'S DISEASE AMYLOID-β PRODUCTION

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Background: Understanding of the role of lipids in AD is growing rapidly, we report here on the most recent identifications of molecular pathways linking lipids with AD aetiology. We found that amyloid-β (Aβ) and the intracellular domain of the Alzheimer's disease amyloid precursor protein (AICD) in brain function as physiological signalling molecules that control activity and expression of lipid metabolic enzymes. *Vice versa*, certain lipids can have a profound effect on amyloid precursor protein (APP) processing and Aβ generation. This primarily involves lipids which play an important role in brain physiology and which are synthesized by neurons and/or glia. Especially, sphingolipids, cholesterol, gangliosides and plasmalogens belong to this group of lipids. The essential polyunsaturated fatty acid docosahexaenoic acid (DHA) had been intensely studied for its neuroprotective potential. The intake of the DHA has been associated with decreased amyloid deposition and a reduced risk in AD in several epidemiological trials; however the exact underlying molecular mechanism remains to be elucidated.

Here we systematically investigated the effect of DHA, cholesterol, sphingolipids, gangliosides and plasmalogens on amyloidogenic and non-amyloidogenic APP processing and potential crosslinks to cholesterol metabolism *in vivo* and *in vitro*. E.g. DHA reduces amyloidogenic processing by decreasing β- and γ-secretase activity, whereas the expression and protein levels of BACE1 and Presenilin1 remain unchanged. In addition, DHA increases protein stability of α-secretase resulting in increased non-amyloidogenic processing. Beside the known effect of DHA to decrease cholesterol *de novo* synthesis, we found cholesterol distribution in plasma membrane to be altered. In presence of DHA, cholesterol shifts from raft to non-raft domains, which is accompanied by a shift in γ-secretase activity. There are several mechanistic links and similarities between the molecular mechanisms employed by the different lipids. E.g. or most lipids a combination of Aβ and AICD is used for homeostatic regulation. This presentation will give an overview of the most recently identified molecular mechanisms and their relevance to the disease process.

Conclusions: Taken together, the biological function of APP is the regulation of lipid levels, in feed-back APP processing is regulated by lipids. Certain dietary lipids and fatty acids increase amyloidogenic APP processing. DHA however, directs processing of APP towards the non-amyloidogenic pathway. DHA has a typical pleiotropic effect; DHA-mediated Aβ reduction is not the consequence of a single major mechanism, but the result of combined multiple effects that make it especially suitable for Alzheimer preventive or early intervention approaches.

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TARGET VALIDATION IN ANIMAL MODELS OF ALZHEIMER'S DISEASE: PROBLEMS WITH TRANSLATION INTO THERAPY?

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Due to the multiple failures of new drugs in progressed clinical development for Alzheimer's disease (AD), in spite of promising preclinical data, there is an increasing doubt in the predictive value of animal models for proof of concept studies. For AD, preclinical studies are in particular challenging, because there is no real naturally occurring animal model. Therefore, either induced models, where lesions, which are believed to be in relation to the disease or at least to symptoms, are utilized or transgenic animal models, where disease-specific, important pathogenic molecules are overexpressed. Both approaches have pros and cons. E.g. cholinergic lesions were successfully used to develop drugs for treatment of AD. After discovery of mutations that are responsible for early onset AD, there was a big hope they can be used to create better animal models resembling AD, which will then allow to develop more specific and disease-modifying treatment approaches. Based on the amyloid cascade theory of AD, most of these models used mutated APP or Presenilin or both. Also, an increasing number of tau tg-rodents is available, and in addition combinations of all these different transgenes, and of additional genetic manipulations to e.g. increase oxidative stress, induce vascular lesions or other alterations of the brain which could be related to aging and dementia. Many compounds have been tested successfully in these models, in particular when the readout was in direct relation to the target, like inhibition of β-secretase. Immunotherapy is a quite typical example for such promising animal studies. The disappointment in human research came mainly from relatively poor or missing clinical improvement, but if target-specific data were evaluated like changes in CSF and plasma Aβ peptides, *post mortem* or *in vivo* brain plaque load, the animal data were well reproduced! At first, this tells us that we should carefully evaluate properties of the failed molecules, and in addition we should rethink the target selection. In conclusion, the animal models predict drug activities in human studies pretty well, a remaining question is if these targets are in direct relationship to the clinical representation of the disease? But of course in addition we have to consider that animal models have to be performed according to strict and standardized procedures to increase predictive value.

THE FINNISH GERIATRIC INTERVENTION STUDY TO PREVENT COGNITIVE IMPAIRMENT AND DISABILITY (FINGER): STUDY DESIGN AND PROGRESS

Miia Kivipelto[1,2,3,4], Alina Solomon[1,3,4], Satu Ahtiluoto[2], Tiia Ngandu[2,4], Jenni Lehtisalo[2], Riitta Antikainen[5], Tuomo Hänninen[6], Antti Jula[2], Tiina Laatikainen[2], Jaana Lindström[2], Francesca Mangialasche[3], Aulikki Nissinen[2], Teemu Paajanen[1], Satu Pajala[7], Markku Peltonen[2], Rainer Rauramaa[8], Timo Strandberg[5], Jaakko Tuomilehto[9,10], Hilkka Soininen[1,6]

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Rationale: Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) is a multi-center randomized controlled trial ongoing in Finland.
Methods: Participants (1200 individuals at risk of cognitive decline) are recruited from previous population-based non-intervention studies. Inclusion criteria are Dementia Risk Score≥6 and cognitive performance at mean level or slightly lower than expected for age (but not substantial impairment) assessed with The Consortium to Establish a Registry for Alzheimer's Disease (CERAD) neuropsychological battery. The 2-year multi-domain intervention consists of nutritional guidance; exercise; cognitive training and social activity; and management of metabolic and vascular risk factors. Persons in the control group get regular health advice. The primary outcome is cognitive performance measured with modified Neuropsychological Test Battery, Stroop, and Trail Making test. Main secondary outcomes are: dementia (after extended follow-up), disability, depressive symptoms, vascular risk factors and outcomes, quality of life, utilization of health resources, and neuroimaging measures.
Results: Screening began in September 2009 and was completed in December 2011. All 1200 persons are enrolled and the intervention is ongoing as planned. Baseline clinical characteristics indicate that several vascular risk factors and unhealthy lifestyle related factors are present, creating a window of opportunity for prevention. The intervention will be completed during 2014.
Conclusions: The FINGER study is at the forefront of international collaborative efforts to solve the clinical and public health problems of early identification of individuals at increased risk of late-life cognitive impairment, and of developing intervention strategies to prevent or delay the onset of cognitive impairment and dementia.

FOCUS ON ANTIOXIDANTS

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Oxidative/nitrosative damage and inflammation are believed to be crucial in Alzheimer's disease (AD) pathogenesis. Vitamin E is the major lipid-soluble, chain-breaking, non-enzymatic antioxidant, which can be of primary importance in the aging brain, since this organ has a high metabolism and relatively few antioxidant enzymatic defenses. α-tocopherol is the congener that has mainly been investigated in relation to AD, but all eight natural vitamin E forms (α-, β-, γ-, δ-tocopherol, α-, β-, γ-, δ-tocotrienol) have potential neuroprotective activity. All congeners act as antioxidants, and each form shows unique biological functions, including anti-inflammatory activity and modulation of signaling pathways that can mediate neurodegeneration. Data about the association of the vitamin E family with AD are scarce, and only α-tocopherol has been tested as therapeutic in AD, with inconsistent results. We examined the relation of all plasma vitamin E forms and markers of vitamin E damage (α-tocopherylquinone, 5-nitro-γ-tocopherol) to mild cognitive impairment (MCI) and AD. In a multicentric study (AddNeuroMed), we showed that reduced plasma levels of all vitamin E forms and increased levels of their oxidative/nitrosative markers may be indicators for the development of MCI and AD. Within the AddNeuroMed cohort, we also showed that the combined analysis of vitamin E plasma levels and automated magnetic resonance (MRI) measures can accurately distinguish AD and MCI cases from cognitively intact (CN) individuals. Additionally, it can prospectively identify MCI cases that progress to a clinical diagnosis of AD after one year.

In two population-based longitudinal studies in older adults (Kungsholmen Project; CAIDE Study), we found a reduced incidence of cognitive impairment and AD in subjects with high plasma levels of different vitamin E forms.

Vitamin E protective effect can be crucial in mitochondria, which are both main source and elective target of free radicals. We studied activity and expression of mitochondrial aconitase (ACO2) in blood-lymphocytes. ACO2 is an essential component of the Krebs-cycle, and it is sensitive to free radicals damage. Compared to CN subjects, ACO2 activity and expression were reduced in AD and MCI. ACO2 activity correlated with plasma levels on non-enzymatic antioxidants, including α-tocopherol. In other cellular models we showed that supplements containing tocotrienols can prevent ACO2 activity reduction promoted by free radicals.

In conclusion, different natural forms of vitamin E can be important in AD in older adults. Thus, all natural vitamin E forms should be considered when studying the association of this micronutrient with cognitive impairment and AD.

DIABETES, ALZHEIMER AND CEREBROVASCULAR PATHOLOGY

Alina Solomon[1,2], Miia Kivipelto[1,2], Tuomo Polvikoski[3], Timo Erkinjuntti[4], Satu Ahtiluoto[5], Maarit Tanskanen[4], Jaakko Tuomilehto[4,6], Raimo Sulkava[7]

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Rationale: Epidemiological studies have shown that diabetes is a risk factor for dementia, both Alzheimer disease (AD) and vascular dementia. Cerebrovascular and neurodegenerative pathologies often occur together and influence each other, especially at older ages. Neuropathological studies on diabetes and AD have had conflicting results: no association, or less tau and amyloid pathology in patients with diabetes, or more pronounced AD-type changes related to diabetes.

Methods: The Vantaa 85+ study included 553 residents living in the city of Vantaa, Finland, and aged 85 years or more in 1991. Survivors were reexamined in 1994, 1996, 1999, and 2001. Autopsies were performed in 291 persons who died during the follow-up (48% of total population). A total of 132 of the formalin-fixed brains were also subjected to postmortem MRI.

Results: When AD and cerebrovascular pathologies were considered separately, people with diabetes had more extensive vascular pathology (particularly larger cerebral infarcts, >4mm diameter), and less AD pathology. However, people with diabetes and small white matter infarcts (1-4mm) had more extensive β-amyloid deposits and neurofibrillary tangles. Similar patterns were found for diabetes, medial temporal atrophy and white matter lesions on MRI.

Conclusions: People with diabetes may have various neuropathological phenotypes. Some types of cerebrovascular pathology in people with diabetes may be related to increased AD pathology.

CARDIOVASCULAR RISK FACTORS, IMPACT OF LIFESTYLE AND GENES

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Both environmental and genetic factors play a role in the pathogenesis of chronic non-communicable diseases, including Alzheimer's disease (AD). It is well known that modifying lifestyles, i.e. diet, smoking, alcohol intake and physical activity could have beneficial effects both on the risk factors and incidence of cardiovascular diseases and type 2 diabetes. With regard to AD risk, current evidence is weaker, but some studies suggest that Mediterranean style diet could help to prevent the development of AD. Besides Mediterranean diet, also folic acid, low or moderate alcohol intake, cognitive activities and physical activity are considered to lower the risk, whereas diabetes, hyperlipidemia in midlife and smoking seem to increase the risk of AD, but the evidence has been considered to be low for all of these associations. The key question is to what extent it is possible to modify the AD risk by lifestyle changes. In this regard, experiences from diet and lifestyle interventions for prevention of CVD and type 2 diabetes could be of benefit.

In the Finnish Diabetes Prevention Study (DPS), the main objective was to find out whether it is possible to prevent type 2 diabetes by healthy lifestyles, i.e. weight reduction, healthy diet and physical activity. The risk reduction was 58 % in the intervention group, and still after 13 years of follow-up, the incidence of diabetes is 40 % smaller in the original intervention group compared to the control group. In the DPS, we have also shown that lifestyle changes may overcome the genetic and familial risk of diabetes. We have also examined in secondary analyses the impact of lifestyles on the cognitive function, and achieving lifestyle goals of DPS associated with better cognitive performance in the DPS participants, except among ApoE4 carriers. In a separate study, we have shown that ApoE4 carriers respond better to dietary fat modification aimed to reduce serum total and LDL-cholesterol than those with the common ApoE3/3 genotype. Diet and other lifestyles could modify e.g. oxidative stress, inflammation, insulin sensitivity, serum lipids and blood pressure, which, on the other hand, are known to associate with AD risk. Early biomarkers for AD would help to test the impact of different diets in prevention of AD, but long-term controlled trials are needed to get definite answer to the question whether AD is preventable by lifestyle changes.

RISK FACTORS FOR ALZHEIMER'S DISEASE – EXPERIENCE FROM CLINICOPATHOLOGICAL POPULATION-BASED COHORT STUDIES

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It is a big mystery how people get sporadic Alzheimer's disease. Risk factors like middle age hypertension, high cholesterol and diabetes have been found. However, most people having those disorders never get demented.

In research of risk factors, one problem is the difficulty of early diagnosis of Alzheimer's disease. Clinicopathological population-based cohort studies are one step forward, because in those studies we can see the association of putative risk factors also to mild neuropathological changes. Also, false positive cases can be excluded. The EClipSE database is composed of data from three existing European prospective population-based cohort studies (www.eclipsestudy.eu). It is hoped that results from the EClipSE study will improve our understanding of the biological substrates of dementia and which factors may be protective or increase risk.

The results show that the role of genetic risk factors in Alzheimer's disease seems to be greater than previously expected. The genotypes can also protect a person from abnormal pathological changes. Influence of genetic factors is transmitted at least partly via second-stage factors, e.g. vascular risk factors.

TOWARDS COMPREHENSIVE MEMORY PROGRAM IN FINLAND

Hilkka Soininen
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Alzheimer's disease and memory diseases have been recognized as a priority in European Union. In 2011, Ministry of Social Affairs and Health in Finland nominated a task force to prepare a proposal for national memory program. In 2012, the National Memory Program 2012-2020 was published. Finland has been lucky to have a good foundation for the program. The challenge of increasing numbers of patients in the coming years has been taken. We have current guidelines of diagnostics and treatment of memory diseases published in "Current treatment" series by Medical Society Duodecim. We have also published "Practices of good care in all phases of Alzheimer's disease" formulated by an expert group. In addition, Finnish Alzheimer Research Society has produced tools for evaluation of patients' cognition, e.g. the Finnish version of CERAD test battery that is in wide use as a screening instrument for memory disorders.

The National Memory Program strongly emphasizes the promotion of brain health, prevention and early diagnosis of memory diseases, as well as timely care, rehabilitation and support – continuing path of care and services. The program also underlines the need for comprehensive research knowledge and strengthening the expertise and education on memory diseases. Now we have the paper that should be translated into practice. We need now investment that will pay itself in future.

REHABILITATION OF PATIENTS WITH MEMORY DISORDERS

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There is growing evidence on effectiveness of various types of rehabilitation among patients with dementia. On early stages, memory decline rehabilitation should be targeted on cognition. Cognitive training, psychosocial rehabilitation and exercise have shown benefits in improving cognition. In mild to moderate stages, rehabilitation should be targeted on functioning and neuropsychiatric symptoms. On mild to moderate stages of dementia, patients benefit from regular, intense and long-term exercise as well as occupational therapist's guidance in daily activities. They can postpone disabilities and improve ability of these families to cope with daily matters. In severe stage, exercise postpones disabilities and prevents falls. Support of case coordinator helps these patients and their families in all stages. Case coordinator empowers families to tell their needs and improves tailoring treatments and services. Case coordinator's work postpones institutionalization, decreases use of services and improves quality of life. Comprehensive geriatric assessment and tailored, multifaceted treatments improve patients' functioning, and postpone admission to institutional care. New rehabilitation models such as those based on improving nutrition or self-management skills of families are being developed.

The core idea in all rehabilitation should be respecting autonomy of these families, family-centeredness, developing cooperation with them, and supporting them to tell their needs and wishes. Effective rehabilitation is based on supporting caregivers' and patients' self-management skills, problem-solving skills, self-efficacy and mastery on every-day life.

Effective rehabilitation modes are still only patchily implemented in service system. Old routines and attitudes, lack of resources and distorted resource allocation hamper implementing new effective models.

MODELLING OF COSTS OF CARE – RESULTS FROM ALSOVA STUDY

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Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cognitive deterioration, impairment of daily activities and neuropsychiatric symptoms. From the public health point of view, AD is an important and increasing health challenge. The disease burden of AD is expected to increase during the next coming decades due to the aging of population.

Due to a heavy disease burden, there is a high level of unmet needs in the treatment of AD. However, due to the cost containment pressures, also the costs of treatments need to be considered before an adaption decision. Nowadays, health economic modeling is increasingly used to inform decision making in health care. Recent economic evaluation activities related to existing AD treatments have mainly concentrated on the evaluation of therapeutic and economic value of cholinesterase inhibitors (ChEIs) or memantine. These evaluations have mainly based on different kinds of decision analytic models, where the standard outcome measure for modeling clinical outcomes has been Mini Mental State Examination (MMSE). MMSE-based cost-effectiveness models, however, have been criticized as not accurately reflecting the total impact of AD (i.e. cognition decline alone may not accurately reflect progression of all the aspects of AD that determine e.g. the probability of institutionalization) and, thus, providing untrustworthy estimates of total treatment benefit. Therefore, more research is needed about measures of AD severity and their ability to explain variation in cognitive, functional, and behavioral measures as well as economic and quality of life outcomes.

The ongoing ALSOVA study - lead by the University of Eastern Finland - provides a unique longitudinal AD dataset, which could be used to improve the economic modeling in AD. The ALSOVA study is a prospective, randomized, and controlled 5-year follow-up study evaluating the effectiveness of early rehabilitation on health-related quality of life and risk of institutionalization in mild AD. Currently, data from the 5-year follow-up visits is expected to be available by the end of year 2012. The ALSOVA study provides valuable dataset to evaluate long-term costs and health outcomes related to the progression of AD, as well as, to determine relationships between patient characteristics, measures of AD progression, probability of institutionalization, and the long-term health and social care utilization, time costs associated with informal caregiving for AD patients in real life circumstances. The development of new cost-effectiveness model based on the findings of the ALSOVA study may draw a more accurate picture of long-term cost-effectiveness of future AD treatments.

Abstracts for poster presentations

Poster board numbers are the same as abstract numbers

P1

CLINICAL CHARACTERISTICS OF *C9ORF72*-LINKED FRONTOTEMPORAL LOBAR DEGENERATION

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Rationale: The most common genetic cause of frontotemporal lobar degeneration (FTLD) and amyotrophic lateral sclerosis (ALS) has been mapped to a repeat expansion in the gene *C9ORF72*. Irrespective of the population, the expansion carriers seem to share the known Finnish founder risk haplotype. In the present study, we provide detailed analysis of the clinical findings on Finnish patients with FTLD caused by the *C9ORF72* expansion.
Methods: A cohort of 73 patients with FTLD, previously screened for the *C9ORF72* expansion, was studied in detail. Demographic and clinical features were evaluated in *C9ORF72* expansion carriers and noncarriers. Neuropsychological tests and brain imaging findings were analyzed in carriers. Neuropathological analysis was conducted on two expansion cases and one noncarrier.
Results: The *C9ORF72* expansion was present in 20/70 (29%) probands. Positive family history (OR 3.5 [95% CI 1.2-10.3]) and concomitant ALS (OR = 10.3 [95% CI 1.9-56.7]) were significantly associated with the expansion, whereas the expansion did not significantly affect onset age or FTLD phenotype. Psychoses were detected in both groups; yet, the difference in frequency distribution was statistically insignificant. Numerous p62-positive but phosphorylated TDP-43-negative neuronal inclusions were detected in cerebellar cortex, and ALS-type spinal cord and brain stem lesions were absent or only mild in both expansion cases. *APOE* ε4 did not seem to cluster among *C9ORF72* carriers.
Conclusions: The suggested *C9ORF72* core phenotype includes prominent behavioral features. We also detected high frequency of neuropsychiatric symptoms, including psychoses. However, the neuropsychiatric phenotype of *C9ORF72* expansion cases did not significantly differ from the noncarriers.

P2

ASSOCIATION STUDY OF GENES INVOLVED IN AMYLOID-β DEGRADATION AND CLEARANCE IN ALZHEIMER'S DISEASE

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Rationale: Alzheimer's disease (AD) is a genetically heterogeneous disorder and it is characterised by the progressive accumulation of amyloid-β peptide (Aβ) in the brain. It is a well-established fact that the accumulation of Aβ in the AD brain is partially caused by defects in its degradation and clearance. Here we have selected 12 genes encoding enzymes or proteases involved in Aβ degradation or clearance to study their genetic association with AD among a Finnish case-control cohort.

Methods: Thirty-one SNPs in 12 genes were selected for genotyping using the *Sequenom* platform. Case-control cohort consisted of altogether ~1300 Finnish AD patients and controls. Cerebrospinal fluid (CSF) levels of Aβ42, total-tau and phospho-tau (p-tau) were correlated with the genetic data.

Results: *APOE*, gender and age-adjusted logistic regression analysis revealed a protective effect for the C allele carriers of rs7120118 in the liver X receptor-α (*NR1H3*) gene (p=0.014; OR=0.70, 95% CI 0.53-0.93). Interestingly, we also detected a significant decrease in CSF p-tau levels among AD patients carrying the C allele of rs7120118 and the A allele of rs2279238 in the *NR1H3* gene. Furthermore, there was a significant increase in the CSF p-tau levels among AD patients carrying the G allele of rs1080093 in transthyretin (*TTR*) gene. We also observed a significant decrease at the age of onset among AD patients carrying the A allele of rs723744 and C allele of rs3794884 in the *TTR* gene.

Conclusions: These results suggest that genetic alterations in *NR1H3* and *TTR* may play a role in AD.

P3

GRN VARIANT rs5848 REDUCES PLASMA AND BRAIN LEVELS OF GRANULIN IN AD PATIENTS

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Rationale: Genetic variants in granulin (*GRN*) gene have been shown to increase the risk of Alzheimer's disease (AD). Since granulins are neurotrophic factors that enhance neuronal survival, decreased levels of granulin have been suggested to cause neurodegeneration. AD patients carrying the A allele have shown reduced granulin levels in plasma and decreased mRNA levels of granulin in the brain and peripheral mononuclear cells.

Methods: Granulin levels in plasma were measured using ELISA in duplicates and results were analysed blinded to diagnosis. DNA samples were genotyped for SNP rs5848 in *GRN* gene using cycle sequencing. Statistical analyses were performed by using SPSS 19.

Results: We have previously shown that the A allele of rs5848 increases the risk for AD in a gender-dependent manner. We found that AD patients had higher plasma granulin levels than controls. Men had lower levels of granulin than women in the whole cohort as well as in AD and control groups. This suggests the idea of gender contributing to the granulin levels.

Conclusions: The A allele of rs5848 reduces the expression of granulin which may increase the susceptibility for AD. Dose-dependent reduction in the granulin levels in plasma and brain due to the A allele of rs5848 corroborate the idea that this variation results in a functional change in *GRN*.

P4

PCSK9 REGULATES NEURONAL APOPTOSIS BY ADJUSTING APOER2 LEVELS AND SIGNALING

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Rationale: Proprotein convertase subtilisin/kexin type 9 (PCSK9) binds to low-density lipid (LDL) receptor family members LDLR, VLDLR and ApoER2 promoting their degradation in intracellular acidic compartments. LDLR controls the systemic levels of circulating LDL, whereas ApoER2 and VLDLR primarily mediate Reelin signaling in the brain, critical for the development and plasticity of the central nervous system. Expression level of PCSK9 is highest in the cerebellum during perinatal development, but is also increased in the ischemic brain. The function of PCSK9 in apoptotic context is currently poorly understood.
Aim: To investigate the role of PCSK9 in neuronal apoptosis.
Methods: Potassium deprivation of cerebellar granule neurons (CGN) was used as an apoptosis model and cell death assessed by activation of caspase-3 and c-Jun and nuclear morphology. PCSK9, VLDLR and ApoER2 were targeted by lentiviral RNAi to investigate their role in CGN apoptosis.
Results: PCSK9 RNAi reduced the activation of c-Jun and caspase-3 by 44% and 59%, respectively, at 6 h post-deprivation and the resulting cell death by 41%. Protection was observed up to 24 hours post-deprivation. RNAi of ApoER2 but not of VLDLR reversed the protection elicited by PCSK9 RNAi. Pharmacological studies suggested that PCSK9 regulates neuronal apoptosis independently of NMDA receptor function but in concert with ERK and JNK signaling pathways. PCSK9 RNAi also protected CGN from staurosporine-induced apoptosis and dorsal root ganglion neurons from NGF-deprivation.
Conclusions: Our results indicate that PCSK9 potentiates neuronal apoptosis via downregulation of ApoER2 levels and related anti-apoptotic signaling pathways.

P5

MOLECULAR MECHANISMS OF SELADIN-1 IN PATHWAYS RELEVANT FOR ALZHEIMER'S DISEASE PATHOGENESIS

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Rationale: Seladin-1/DHCR24 is a neuroprotective protein selectively down-regulated in brain regions affected in Alzheimer's disease (AD). Seladin-1 confers resistance against Aβ- and oxidative stress-induced apoptosis. Decreased levels of seladin-1 lead to the increased β-amyloidogenic processing of amyloid precursor protein (APP) in apoptotic conditions. Collectively, these data suggest that seladin-1 has an important role in the AD pathogenesis.
Methods: Here, we investigated whether the over-expression of seladin-1 has beneficial effects on pathways relevant for AD, such as APP processing and Aβ generation in human SH-SY5Y neuroblastoma cells over-expressing APP751 isoform (SH-SY5Y-APP751). SH-SY5Y-APP751 cells were transfected with *SELADIN-1* containing plasmid and after 48 hours total protein lysates as well as cell culture medium samples were analyzed using Western blotting and Aβ ELISA.
Results: Over-expression of seladin-1 significantly increased the levels of total APP on average 1.6-fold. Conversely, total APP-normalized APP C-terminal fragment levels were decreased, which again coincided with the decreased Aβ40 and Aβ42 levels in the cell culture medium.
Conclusions: These results suggest that elevated seladin-1 expression in neuronal cells may exert beneficial effects on APP processing by reducing Aβ generation.

P6

γ-AMINOBUTYRIC ACID TYPE A ($GABA_A$) RECEPTOR ACTIVATION MODULATES TAU PHOSPHORYLATION

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Rationale: Abnormal phosphorylation and aggregation of the microtubule-associated protein Tau are hallmarks of various neurodegenerative diseases, such as Alzheimer's disease (AD). Tau phosphorylation regulates its functions and is increased in AD. Molecular mechanisms that regulate Tau phosphorylation are complex and currently incompletely understood. Peptidyl-prolyl *cis-trans*-isomerase 1 (Pin1) is a critical regulator of Tau dephosphorylation at several disease-associated proline-directed phosphorylation sites. Reduced Pin1 activity has been associated with Tau hyperphosphorylation *in vitro* and *in vivo*.
Methods: We have developed a novel live-cell reporter system based on protein-fragment complementation assay (PCA), using split humanized *Gaussia princeps* luciferase (hGLuc), to study dynamic changes in Tau phosphorylation status. In this assay, fusion proteins of Tau and Pin1 carrying complementary fragments of the hGLuc protein serve as a sensor of altered protein-protein interaction between Tau and Pin1.
Results: We identified several structurally distinct $GABA_A$ receptor modulators as novel regulators of Tau phosphorylation in a chemical library screen. $GABA_A$ receptor activation promoted specific phosphorylation of Tau at the AT8 epitope (Ser-199/Ser-202/ Thr-205) in cultures of mature cortical neurons. Increased Tau phosphorylation by $GABA_A$ receptor activity was associated with reduced Tau binding to protein phosphatase 2A and was dependent on Cdk5 but not GSK3β kinase activity.
Conclusions: (1) $GABA_A$ receptor activity is associated with regulation of Tau phosphorylation. (2) hGLuc-based PCA is an efficient novel method for studying Tau interactome dynamics and for high-throughput screening of modulators of Tau function in live cells.

P7

UBIQUILIN-1-INDUCED ACCUMULATION OF PRESENILIN-1 INTERFERES WITH PI3K/Akt SIGNALING PATHWAY AND AFFECTS GSK3 ACTIVITY

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Rationale: Ubiquilin-1 is a protein, which is both genetically and functionally associated with Alzheimer's disease (AD). We have previously demonstrated that ubiquilin-1 transcript variants 1 (TV1) and 3 (TV3) regulate the accumulation of full-length presenilin-1 (PS1) in aggresomes. PS1 is the catalytic subunit of γ-secretase complex, which generates amyloid-β peptide from amyloid precursor protein (APP). On the other hand, PS1 promotes cell survival independently of γ-secretase activity by activating the PI3K/Akt signaling pathway. As a consequence, GSK3β-dependent phosphorylation of tau is suppressed. However, lack of PS1 or familial AD-related *PSEN1* mutations inhibit the PS1-dependent PI3K/Akt signaling, thus promoting hyperphosphorylation of tau. Here, we have investigated the effects of ubiquilin-1-induced accumulation and aggresomal targeting of PS1 on PI3K/Akt signaling and GSK3 activity.
Methods: We used transient transfection of PS1 together with myc-TV1-mRFP, myc-TV3-mRFP, or mRFP control plasmid in HEK293 cells stably overexpressing APP conjugated to alkaline phosphatase (HEK293-AP-APP). Western blotting and specific antibodies were used to visualize TV1, TV3, and PS1 and phosphorylated and total forms of Akt, GSK3α and GSK3β.
Results: Ubiquilin-1 TV1 and TV3 co-overexpression with PS1 significantly decreased Akt phosphorylation but not total Akt levels in HEK293-AP-APP cells, suggesting decreased Akt activation. As a downstream effect, inhibitory phosphorylation of GSK3α and GSK3β was decreased while total levels of these proteins remained unaltered.
Conclusions: Our results suggest that ubiquilin-1 TV1- and TV3-induced accumulation of PS1 can interfere with PI3K/Akt signaling. Consequently, this may result in tau hyperphosphorylation and compromised cell survival.

P8

UBIQUILIN-1 MODULATES AMYLOID PRECURSOR PROTEIN PROCESSING AND γ-SECRETASE-MEDIATED ε-CLEAVAGE IN NEURONAL CELLS

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Rationale: Ubiquilin-1 is genetically and functionally associated with Alzheimer's disease. Ubiquilin-1 full-length transcript variant 1 (TV1) modulates amyloid precursor protein (APP) processing, amyloid-β (Aβ) secretion and presenilin-1 (PS1) accumulation. Here, we have elucidated the molecular mechanisms behind the effects of ubiquilin-1 underlying altered APP processing and γ-secretase function.
Methods: SH-SY5Y human neuroblastoma cells stably over-expressing APP751 isoform (SH-SY5Y-APP751) were transiently transfected with plasmids encoding TV1, myc-TV1, myc-TV2, FE65, FL-LAR-V5-His or control plasmids. Western blotting, *in vitro* AICD generation assay, cell-surface biotinylation assay and confocal microscopy were used to assess alterations in APP processing and γ-secretase activity.
Results: TV1 over-expression increased APP maturation and APP C-terminal fragment levels. Levels of total secreted APP and APP intracellular domain (AICD) were concomitantly increased. Although the AICD generation significantly increased upon TV1 expression, the Aβ levels increased only modestly, suggesting that TV1 particularly modulates the γ-secretase-mediated ε-site cleavage of APP. Over-expression of TV1 along with another γ-secretase substrate, leukocyte common antigen related phosphatase (LAR), resulted in competition between APP and LAR for γ-secretase cleavage. TV2, another ubiquilin-1 variant which lacks exon 8, also affected APP processing, but did not modulate γ-secretase cleavage. Mechanistically, the effects of TV1 were not mediated by FE65, which has been suggested to regulate AICD generation and stability. While the subcellular localisation of APP or γ-secretase complex components was not altered, N-terminal APP partially co-localised with TV1 in ubiquitin-positive LC3B-negative cytoplasmic structures.
Conclusion: Collectively, these data suggest that ubiquilin-1 modulates APP processing and γ-secretase-mediated ε-cleavage in neuronal cells.

P9

PRO-INFLAMMATORY INTERLEUKIN-18 DIRECTLY INCREASES ALZHEIMER'S DISEASE ASSOCIATED AMYLOID-β IN HUMAN NEURON-LIKE CELLS

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Rationale: Alzheimer's disease (AD) involves increased accumulation of amyloid-β (Aβ) plaques and neurofibrillary tangles as well as neuronal loss in various regions of the neocortex. Neuroinflammation is also present, but its role in AD requires clarification. We previously showed increased levels of pro-inflammatory Interleukin-18 (IL-18) in different regions of AD brains, where it co-localized with Aβ-plaques. Elevated IL-18 has been detected in several risk conditions for AD, including obesity, type-II diabetes, cardiovascular diseases and in stress.
Methods: Differentiated SH-SY5Y neuroblastoma cells were exposed to IL-18 for various times. The protein levels Aβ-precursor protein (APP) and its processing products, APP cleaving enzymes and markers of apoptosis were examined.
Results: IL-18 increased protein levels of BACE1 and the members of the γ-secretase complex, the N-terminal fragment of presenilin-1 and presenilin enhancer 2 slightly. IL-18 also increased APP expression and phosphorylation, which preceded increased BACE1 levels. Further, IL-18 altered APP processing, increasing Aβ production, which was inhibited by IL-18 binding protein. Increased levels of soluble APPβ were detected in culture medium after the IL-18 exposure.
Conclusions: IL-18 has a direct impact on Aβ production, contributing to Aβ-plaque formation and the pathogenesis of AD. However, the IL-18 induction of BACE1, APP processing and Aβ is likely to be linked to stress-associated adaptations in neurons during the course of normal functioning and development. In the aged brain, the effects of heightened or prolonged levels of IL-18 will likely contribute to the process of neuronal loss, including via increased Aβ.

P10

INTERLEUKIN-18 DECREASES LEVELS OF PEROXIREDOXINS, INVOLVED IN ALZHEIMER'S DISEASE, IN NEURON-LIKE SH-SY5Y CELL CULTURE MODEL

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Rationale: Alzheimer's disease (AD) brain has signs of chronic inflammation and oxidative stress, sustained by inflammatory cytokines, in addition to classic amyloid-β plaques and neurofibrillary tangles. According to our previous findings, expression of pro-inflammatory Interleukin-18 (IL-18) is enhanced in the AD brain. Therefore, we used IL-18 for differentiated SH-SY5Y neuroblastomas and found in two-dimensional difference-gel-electrophoresis and mass spectrometry analyses that expression of Peroxiredoxins (Prxs) II, -III and -VI were altered after IL-18 treatments. Prxs are a family of multifunctional antioxidant thioredoxin-dependent peroxidases, which comprise cellular protection against oxidative stress. At least PrxIII levels have been shown to be decreased in AD brain.

Methods: Differentiated SH-SY5Y cells were treated with IL-18 for varied times and the cell lysates were analysed with Western blots to verify the protein levels of Prxs. The protein expression of mitochondrial bcl-xL and the activity of Lactate dehydrogenase (LDH) were also analysed.

Results: We found that protein levels of cytosolic PrxII and mitochondrial PrxIII decreased in 72h IL-18-treated SH-SY5Y-cells compared to untreated controls (mean -23.5%, SEM ±7.96, n5, p=.005) and (-26.8% ±7.48, n15, p=.020), respectively. Cytosolic PrxVI decreased earlier, in 24h and 48h time-points (-14.5% ±6.24; n15; p=.003) and (-23.2% ±7.28; n15; p=.003), respectively. Bcl-xL levels reduced during 6h IL-18-treatment but increased in 72h time-point (23.5% ±23.5; n14; p=.039). However, activity of LDH in culture media was unaltered.

Conclusion: IL-18 can induce reduction of antioxidative Prxs in neuron-like cells in coordinated manner suggesting increased oxidative stress, which may be counteracted by neuroprotective and by oxidative stress regulated bcl-xL.

P11

PROTEOMICS TO CHARACTERIZE ASTROCYTE ACTIVATION

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Rationale: Microglia activates astrocytes into inflammatory cells. We have examined the proteome changes in normal human astrocytes (NHAs) stimulated with cytokines that are known to be secreted by microglia, and to induce inflammatory changes in astrocytes. After cytokine priming, the cells were left unstimulated or activated with Poly(I:C), a mimetic of viral double-stranded RNA, which activates Toll-like-receptor 3 (TLR3).
Methods: For the experiment, NHAs (Clonetics) were starved in serum-free medium and treated with IL-1β, TNF-α, and IFN-γ for 24h followed by stimulation with Poly(I:C) for 6 h. Proteome changes in whole cell lysates were quantitatively assessed using 4plex iTRAQ labeling combined with liquid chromatography-tandem mass spectrometry.
Results: Cytokine stimulation resulted in morphological changes in astrocytes. Following TLR3 stimulation-induced cell death in NHAs, a total of 1136 proteins were identified and 862 quantified. From these, 18 were upregulated and two downregulated after cytokine stimulation and 22 upregulated and three downregulated after stimulation with cytokines and dsRNA. Differentially regulated proteins were linked to various biological processes, however, the most represented pathways were associated with cytokine-mediated signaling (i.e. ICAM1, ISG15, IFIT 1 and 3).
Conclusions: Our current results suggest that TLR3 stimulation alone does not trigger significant changes in NHA proteome. In contrast, cytokine stimulation alone and in combination with TLR3 signaling resulted in both morphological and proteome alterations in NHAs.

P12

POST-TRAUMATIC EPILEPTOGENESIS IN APP/PS1 MOUSE MODEL WITH AMYLOIDOGENIC APP PROCESSING

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Rationale: Growing evidence suggests an association between Alzheimer's disease (AD) and epilepsy. It has been shown that 65% of APP/PS1 mice display at least one seizure by the age of 5 months. To elaborate the role of increased amyloid load in epileptogenesis, we investigated whether traumatic brain injury (TBI), a risk factor for AD, facilitates epileptogenesis in AD mouse model.
Methods: TBI was triggered in 13-15wk old male APP/PS1 mice and wild type (Wt) littermates. Motor recovery was assessed with Neuroscore at 2, 7, 14d post-TBI. Spatial memory was evaluated using Morris water-maze (MWM). Then, mice were followed-up for 2-wk with continuous video-EEG monitoring starting at 6wk and 14wk post-TBI.
Results: AD injured showed motor deficits compared to AD controls at 2d ($p<0.01$), 7d ($p<0.01$) and 14d post-TBI ($p<0.05$). AD injured were more impaired than Wt injured at 14d post-TBI ($p<0.01$). Acquisition in MWM was longer in AD injured than in Wt injured group ($p<0.05$). In 1stEEG recording 86% of AD injured develop spontaneous seizures compared to 36% in AD shams ($p<0.05$) and 7% in Wt injured ($p<0.001$). Epileptiform discharges (EDs) were observed in 21% of AD injured and 36% of AD shams, whereas in Wt group, 20% of injured but none of sham-operated displayed EDs.
Conclusions: Our data show that TBI triggers epileptogenesis both in Wt and AD mice. However, post-traumatic epileptogenesis was more pronounced in APP/PS1 and associated with more severe co-morbidities (motor deficits, spatial learning and memory) compared to Wt mice. Whether this relates to TBI-triggered increased amyloidogenesis is under investigation.

P13

THE EFFECTS OF AXONAL DAMAGE ON AMYLOIDOGENIC APP AND TAU PROCESSING IN THE POST-TRAUMATIC EPILEPSY

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Rationale: About 10-20% of acquired epilepsy is caused by traumatic brain injury (TBI). TBI-associated axonal injury triggers amyloidogenesis and altered tau levels both in animals and humans which have been suggested to contribute to poor cognitive recovery. Previous studies in mouse models of Alzheimer's disease (AD) suggest a link between amyloidogenic amyloid precursor protein (APP) processing, tau, and hyperexcitability. Here we hypothesized that AD-like pathology after TBI may associate with post-traumatic epileptogenesis.

Methods: TBI was induced by lateral fluid-percussion injury to adult male Sprague-Dawley rats. Rats were decapitated 2, 7, or 60 days after TBI and consequently cerebral cortex, thalamus and hippocampus were dissected bilaterally. The levels of GGA3, BACE1 (β-secretase), APP, T-Tau, P-Tau, Scn2β, Scn4β and GAPDH were determined using Western blotting. Aβ levels from the cortex and thalamus were assessed using the Aβ1-40 and Aβ1-42 ELISA kits.

Results: In the ipsilateral cortex, BACE1 and Total-Tau levels were increased an average 3-fold after 2 days of TBI. Increase in BACE1 levels coincided with the depletion of full-length GGA3 and with the increased production of Aβ42 and Aβ40. At this time point, Scn4β levels were found to be decreased in the ipsilateral cortex. After 60 days of TBI, the levels of APP C-terminal fragments were significantly increased in the ipsilateral thalamus. In conjunction, calcium and Aβ42 levels were also augmented.

Conclusions: These data warrant functional analysis whether post-TBI amyloidogenesis, regulation of expression of BACE1 and Na-channel β4 subunit as well as increased calcium load contribute to post-TBI hyperexcitability.

P14

SPONTANEOUS SEIZURES IN ARCTIC APP TRANSGENIC MOUSE MODEL OF ALZHEIMER'S DISEASE

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Rationale: The pathogenic Arctic mutation of amyloid precursor protein (E693G) has been identified in family with early-onset Alzheimer's disease (AD). APParc mutation increases amyloid-β (Aβ) protofibril formation leading to accumulation of insoluble intra- and extra-cellular Aβ. That process has been hypothesized as a major mechanism that contributes to AD in Arctic mutation carriers. Transgenic mice with neuron-specific expression of human APParc were created to study the effects of mutation. APParc mice show unexpected episodes of abnormal behavior, also colony mortality was high. We assumed the presence of epileptic seizures and performed long-term video-EEG study.

Methods: 21 homozygous APParc tg female mice and their 11 wt littermates were implanted with cortical electrodes. 3 video-EEG sessions (24/7, 2 wk) were done at age of 3.5 – 4.5 month, 5.5 month and 7.5 – 8 month. The behavioral phenotype of the seizure was assessed with Racine's scale.

Results: At the age of 3.5 – 4.5 months, 6/21 (29%) APParc tg mice and in 2/11 (18%) wt mice had spontaneous seizures. At age of 5.5 months, seizures were observed in 6/20 (30%) APParc tg (2 mice with new-onset seizures) and in 2/11 (18%) wt (2 mice with new-onset seizures). Seizure frequency was 1 seizure per 2 wk, seizure duration in APParc tg mice was 18±10 sec in Session 1 and longer (33±17 sec, $p<0.05$) in Session 2.

Conclusion: APParc mutation increases risk of development of spontaneous seizures in AD mouse. Our model might be useful to study mechanisms by which Aβ processing abnormalities affect neuronal excitability.

P15

INCREASED CORTICAL AND THALAMIC EXCITABILITY IN FREELY MOVING APP_{SWE}/PS1dE9 MICE MODELING EPILEPTIC ACTIVITY ASSOCIATED WITH ALZHEIMER'S DISEASE

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Rationale: Amyloid precursor protein transgenic mice modeling Alzheimer's disease display frequent occurrence of seizures peaking at an age when amyloid plaques start to form in the cortex and hippocampus. We tested the hypothesis that numerous reported interactions of amyloid-β with cell surface molecules result in altered excitation-inhibition balance in brain-wide neural networks, eventually leading to epileptogenesis.
Methods: We examined electroencephalograms (EEGs) and auditory evoked potentials (AEPs) in freely moving 4-month-old APPswe/PS1dE9 (APdE9) and wild-type (WT) control mice in the hippocampus, cerebral cortex and thalamus during movement, quiet waking, NREM sleep and REM sleep.
Results: Consistent with earlier studies, amyloid plaques only started to build up in 5-month-old APdE9 mice (corresponding to ~0.1% amyloid plaque load at this age). Cortical EEG power was higher in APdE9 mice than WT mice over a broad frequency range (5-100 Hz) and during all four behavioral states. Thalamic EEG power was also increased but in a narrower range (10-80 Hz). Furthermore, APdE9 mouse displayed augmented cortical and thalamic AEPs. While power and theta-gamma modulation was preserved in the APdE9 hippocampus, REM sleep-related phase shift of theta-gamma modulation was altered. In addition, we describe new electrophysiological phenomena, which will help characterization of ongoing physiological processes and understanding of coupling mechanisms within and between brain regions.
Conclusions: Our data suggest that at the early stage of amyloid pathology cortical principal cells become hyperexcitable and via extensive cortico-thalamic connection drive thalamic cells. The minor hippocampal changes are most likely secondary to abnormal entorhinal input.

P16

DIFFERENT EFFECT OF CHRONIC AND ACUTE ADMINISTRATION Aβ PEPTIDE ON SYNAPTIC PLASTICITY IN HIPPOCAMPAL SLICES OF APP/PS1 TRANSGENIC MICE

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Rationale: The importance of small soluble Aβ oligomers in AD pathology is emphasized by the finding that soluble Aβ levels in AD brain correlate much better with cognitive decline than the number or volume of amyloid plaques (AP). Here we compared two forms of Aβ oligomers administration on hippocampal synaptic plasticity.
Methods: The effect of chronic form (generated by human mutated APPswe/PS1dE9 gene) was tested in slices from 5-month-old APdE9 and wild-type control mice. The effect of acute Aβ oligomer administration (synthetic) was tested in pre-incubated slice. In addition, we tested the hypothesis that AP function as drains that collect toxic Aβ oligomers and protect neurons from their harmful effects.
Results/Conclusions: An externally applied oligomeric Aβ peptide caused reduction of slices excitability or excitatory drive to CA1 cells as measured by reduced basal synaptic transmission, diminished fEPSP amplitude and increased current to elicit population spike. In addition, long-term potentiation (LTP) was suppressed in slices with externally applied oligomeric Aβ peptide. Especially vulnerable is late phase of LTP (after 20 min). In contrast, 'endogenous mix of Aβ peptides' did not affect CA1 principal cell excitability or LTP induction and maintenance, but paired-pulse facilitation, as measurement of short-term plasticity, was suppressed at smaller inter-stimulus intervals (20-50 ms) in APdE9 mice. Contrary to our expectation, at early phase of AP formation (~ 0.1% load at 5-months-old), deposits have neither protective nor unfavorable effect with regards to externally applied oligomeric Aβ peptide as we observed little interaction of those two factors on measured parameters.

P17

EFFECTS OF HUMAN INTRAVENOUS IMMUNOGLOBULIN ON AMYLOID PATHOLOGY AND NEUROINFLAMMATION IN A MOUSE MODEL OF ALZHEIMER'S DISEASE

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Rationale: Human intravenous immunoglobulin (hIVIG) preparation is indicated for treating primary immunodeficiency disorders associated with impaired humoral immunity. hIVIG is known for its anti-inflammatory properties and a decent safety profile. Therefore, by virtue of its constituent natural anti-amyloid-β antibodies and anti-inflammatory effects, hIVIG is deemed to mediate beneficial effects to patients of Alzheimer's disease (AD). Here, we set out to explore the effects of hIVIG in a mouse model of AD.

Methods: We treated APP/PS1dE9 transgenic and wild-type mice with weekly injections of a high hIVIG dose (1 g/kg) or saline for 3 or 8 month duration. Treatment effect on brain amyloid pathology and microglial reactivity was assessed by ELISA, immunohistochemistry, RT-PCR and confocal microscopy.

Results: We found no evidence for reduction in Aβ pathology; instead 8 months of hIVIG treatment significantly increased soluble levels of Aβ40 and Aβ42. In addition, we noticed a significant reduction in CD45 and elevation of Iba-1 markers in specific sub-populations of microglial cells. Long-term hIVIG treatment also resulted in significant suppression of TNF-α and increase in doublecortin-positive adult-born neurons in the dentate gyrus.

Conclusions: Our data indicates limited ability of hIVIG to impact amyloid burden but shows changes in microglia, pro-inflammatory gene expression and neurogenic effects. Immunomodulation by hIVIG may account for its beneficial effect in AD patients.

P18

NONSELECTIVE CALCIUM CHANNEL BLOCKER BEPRIDIL DECREASES SECONDARY PATHOLOGY IN $hAPP_{SL}$ MICE AFTER CORTICAL LESION

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Rationale: Experimental studies have identified a complex link between brain ischemia, β-amyloid (Aβ) and calcium homeostasis. The aim of the present study was to further examine this interaction in transgenic $hAPP_{SL}$ mice.
Methods: Transgenic $hAPP_{SL}$ (n=33) and non-transgenic (n=30) male mice (4-5 months old) were subjected to cortical photothrombosis and treated with nonselective calcium channel blocker, bepridil (50 mg/kg, p.o., once a day) or vehicle for 28 days. After the follow-up, animals were perfused for histological analysis of infarct size and Aβ and calcium accumulation in the thalamus.
Results: Cortical photothrombosis resulted in a small infarct, which was associated with a delayed Aβ and calcium accumulation in the ipsilateral thalamus. Ischemia-induced Aβ ($P<0.01$) and calcium ($P<0.01$) accumulation in the thalamus was lower in transgenic mice compared to non-transgenic vehicle-treated mice. Bepridil decreased both Aβ ($P<0.05$) and calcium ($P<0.01$) load in non-transgenic mice. The number of plaques in the cortex seemed to be lower in bepridil-treated transgenic mice. Transgenic bepridil-treated mice had significantly smaller infarct volumes than non-transgenic littermates ($P<0.05$).
Conclusions: The present data suggest less pronounced primary and secondary pathology in $hAPP_{SL}$ transgenic mice after cortical injury. Bepridil decreased both Aβ and calcium pathology in the thalamus following ischemia.

P19

BEPRIDIL DECREASES Aβ AND CALCIUM LEVELS IN THE THALAMUS AFTER MIDDLE CEREBRAL ARTERY OCCLUSION IN RATS

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Rationale: Alzheimer's disease and cerebral ischemia share similar features in terms of altered amyloid precursor protein (APP) processing and β-amyloid (Aβ) accumulation. Related to this, we have previously observed that Aβ and calcium deposition are robustly increased in the ipsilateral thalamus after transient middle cerebral artery occlusion (MCAO) in rats. Importantly, these changes coincided with altered β-secretase levels and activity in the ipsilateral thalamus. Here we have investigated whether chronic treatment with bepridil, a non-selective calcium channel blocker, affects Aβ and calcium levels in the thalamus and in turn functional recovery after transient MCAO in rats.
Methods: Eighteen male Wistar rats were subjected to sham-operation or transient MCAO. Twenty-seven-day administration of bepridil (50 mg/kg/day, *per os*) or the vehicle was started two days after MCAO. Cylinder and tapered/ledged beam walking tests were used as behavioural outcome measures. After the follow-up, animals were sacrificed for analysis of Aβ40, Aβ42, and calcium levels in the contra- and ipsilateral thalami.
Results: Bepridil treatment improved forelimb use in MCAO rats in the cylinder test, which coincided with decreased calcium and soluble Aβ40 and Aβ42 levels in the ipsilateral thalamus when compared to vehicle-treated MCAO rats. Bepridil treatment did not affect astrogliosis or TNFα expression in the ipsilateral thalamus.
Conclusions: These findings suggest that bepridil treatment of MCAO rats decreases soluble Aβ and calcium levels in the thalamus, which coincide with improved sensorimotor recovery.

P20

IMMEDIATE AND POSTPONED EFFECTS OF MICROINJECTION OF α-SYNUCLEIN ON DOPAMINE OVERFLOW IN DORSAL STRIATUM

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Rationale: α-synuclein (α-syn) is a protein that has been implicated in Parkinson's disease and various other neurodegenerative disorders, collectively known as synucleopathies. α-syn pathology is also found in both sporadic and familial cases with Alzheimer's disease. Evidence obtained in knockout mice suggests that α-syn controls plasticity of dopamine overflow in presynaptic terminals. According to the pathogenic protein seeding theory, the spreading of pathology in synucleopathies and Alzheimer's disease involves seeding of pathogenic proteins and/or their aggregates from cell to cell. Exposure of cells to exogenous α-syn has been used to maintain the theory, but the effects of seeding on neurotransmitter overflow are yet undiscovered.
Methods: We addressed the questions above by performing microinjections of pure human α-syn into the dorsal striatum of wild-type and α-syn knockout mice. Stimulated dopamine release was measured using constant potential amperometry.
Results: Stimulated dopamine overflow was selectively decreased six days after α-syn microinjection in the knockout mice but not in wild-type mice. An increase in stimulated dopamine overflow was found when studying the immediate effects of α-syn microinjection in the knockout mice.
Conclusions: We conclude that exogenous human α-syn protein, delivered using microinjection, can be functional in the murine striatum. The exogenous α-syn causes different effects on dopamine overflow, depending on the length of exposure and presence of endogenous α-syn.

P21

PLASMA HOMOCYSTEINE IN RELATION TO CORTICAL DEPOSITION OF β-AMYLOID AND NEUROFIBRILLARY TANGLES: A POPULATION-BASED NEUROPATHOLOGIC STUDY

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Rationale: Elevated plasma homocysteine (tHcy) concentrations have been linked to dementia. The relationship between tHcy and neuropathologic outcomes such as β-amyloid and neurofibrillary tangles has not been investigated previously.
Methods: The Vantaa 85+ Study included all 601 persons, at least 85 years of age, who were living in Vantaa, Finland, on April 1, 1991. Autopsy data were available for 253 subjects who died during follow-up. Macroscopic infarcts were identified from 1-cm coronal slices of cerebral hemispheres, 5-mm transverse brainstem slices, and sagittal cerebellum slices. Neocortical β-amyloid load and number of neurofibrillary tangles were determined on tissue sections by methenamine silver staining and a modified Bielschowsky staining for neuritic plaques, respectively. Logistic regression models were used to analyze the associations of baseline tHcy with neuropathology.
Results: Individuals with elevated tHcy values were more likely to have higher neurofibrillary tangles counts after all adjustments: the odds ratio (ORs) (95% confidence interval [CI]) for the highest quartile of baseline tHcy compared to the lowest was 2.96 (1.43 – 6.14). This association remained when restricting the subjects to those without any macroscopic infarcts: the OR (95% CI) for the highest quartile of tHcy was: 3.56 (1.15 – 11.04). No relationships between plasma tHcy and β-amyloid protein load or cerebral infarcts were detected.
Conclusions: Higher plasma tHcy was associated with increased neurofibrillary tangles counts, particularly among those without any cerebral infarcts, suggesting a more direct mechanism rather than vascular related mechanisms. Randomized controlled trials are needed to determine the impact of tHcy lowering treatments on neuropathologic outcomes involved in dementia development.

P22

PLASMA VITAMIN D IN RELATION TO COGNITIVE IMPAIRMENT AND CSF BIOMARKERS

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Rationale: The association between vitamin D and cognitive impairment has been investigated by only a few studies and the results have been mixed. Our objective is to investigate the relations between plasma levels of 25-Hydroxyvitamin D (25(OH)D) and cognitive impairment, cerebrospinal fluid (CSF) biomarkers, and structural brain changes.

Methods: 75 patients (29 with subjective cognitive impairment--SCI; 28 with mild cognitive impairment--MCI; 18 with Alzheimer's disease--AD) referred to the Memory Clinic at Karolinska University Hospital, Huddinge, Sweden. Plasma 25(OH)D, CSF levels of $A\beta_{1-42}$, t-tau, and p-tau_{181}, and brain tissue volumes have been measured.

Results: Higher concentrations of 25(OH)D were associated with a better cognitive status: the odds ratios (ORs) (95% confidence interval [CI]) in an ordinal logistic regression analysis was: 0.980 (0.964 – 0.997) per increase of 1 nmol/L of plasma 25(OH)D. Adjustment for several potential confounders did not alter the associations: OR (95% CI) became 0.957 (0.929 - 0.987). In a multiple linear regression analysis, higher 25(OH)D levels were related to higher concentrations of $A\beta_{1-42}$ and white matter volumes: relative difference (95% CI) was: 1.33 (1.01 – 1.74) for $A\beta_{1-42}$ and 1.15 (1.02 – 1.29) for white matter volumes. The associations between 25(OH)D and t-tau, p-tau_{181}, or grey matter volumes were not significant.

Conclusions: This study suggests that plasma vitamin D has an independent association with cognitive status, $A\beta_{1-42}$ profile, and white matter volume. Randomized controlled trials are needed to determine the impact of vitamin D supplementation on preventing cognitive decline and Alzheimer's disease.

P23

CLASSIFICATION AND PREDICTION OF CLINICAL ALZHEIMER'S DIAGNOSIS BASED ON MRI AND PLASMA VITAMIN E MEASURES

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Rationale: To evaluate the accuracy of combined structural MRI measures and plasma levels of vitamin E forms - including all eight natural vitamin E congeners (four tocopherols, four tocotrienols) and markers of vitamin E oxidative/nitrosative damage - in differentiating Alzheimer's disease (AD) and mild cognitive impairment (MCI) cases from cognitively intact individuals (CTL).

Methods: 81 AD cases, 86 MCI and 86 CTL individuals were enrolled from the AddNeuroMed project, a longitudinal multicenter study. MRI and plasma vitamin E data were acquired at baseline. MRI scans were analyzed using Freesurfer, an automated segmentation scheme which generates regional volume and cortical thickness measures. Orthogonal partial least squares to latent structures (OPLS), a multivariate data analysis technique, was used to analyze MRI and vitamin E measures in relation to AD and MCI diagnosis.

Results: The joint evaluation of MRI and plasma vitamin E measures enhanced the accuracy in differentiating AD and MCI from CTL individuals: the accuracy was 98.2% (sensitivity 98.8%, specificity 97.7%) for AD vs. CTL and 90.7% (sensitivity 91.8%, specificity 89.5%) for MCI vs. CTL. This combination of measures also identified 85% of the MCI subjects who converted to clinical AD at 1 year follow-up.

Conclusions: Vitamin E plasma levels and automated MRI measures can help differentiating AD and MCI from cognitively intact subjects, and to prospectively predict MCI conversion. Our results suggest the potential role of nutrient biomarkers detected in plasma - vitamin E forms - as an indirect indicator of AD pathology, and the utility of a multimodality markers approach.

P24

N4U: A WEB-BASED GATEWAY TO NEUROIMAGING RESEARCH

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Rationale: The unprecedented growth, availability and accessibility of sophisticated image analysis algorithms and powerful computational resources led to the idea of developing web-based computational infrastructures that could meet users' new requirements. On the other hand, the gap between the pace of data generation and the capability to extract clinically or scientifically relevant information is rapidly widening.
Methods: Integration of the power of sophisticated mathematical models, efficient computational algorithms and advanced hardware infrastructure provides the necessary sensitivity to detect, extract and analyze subtle, dynamic and distributed patterns distinguishing one brain from another, and a diseased brain from a normal brain.
Results: neuGRID is the leading e-Infrastructure where neuroscientists can find core services and resources for brain image analysis. The neuGRID platform makes use of grid services and computing, and was developed with the final aim of overcoming the hurdles that the average scientist meets when trying to set up advanced experiments in computational neuroimaging, thereby empowering a larger base of scientists. Although originally built for neuroscientists working in the field of AD, the infrastructure is designed to be expandable to services from other medical fields (*e.g.* multiple sclerosis, psychiatric conditions).
Conclusions: "neuGRID for Users" will provide an e-Science environment by further developing and deploying the neuGRID infrastructure to deliver a Virtual Laboratory offering neuroscientists access to a wide range of datasets and algorithm pipelines, access to computational resources, services, and support. Information from this abstract is intended to make aware researchers working with neuroimaging of all possibilities when it comes to resources.

P25

A VOXEL-BASED COMPATIBILITY ASSESSMENT OF THE ADNI-RELATED AND ADNI-GO SCANNING PROTOCOLS.

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Rationale: The new ADNI-GO MRI protocols were designed to be compatible with those that were originally created for ADNI. However, a separate set of ADNI protocols were designed for sites that had a GE scanner but were not part of ADNI (ADNI-related). The aim of the current study was to investigate the compatibility of the ADNI-related (ADNI-R) and ADNI-GO scanning protocols.

Methods: Images of 30 subjects (15-male, mean age 32.2 years and 15-female, mean age 25.1) were acquired on a 3T GE scanner using the following sequences: ADNI-R parameters: Sagittal 3D-IR-FSPGR, 8-channel coil, TR=650ms, TE=min full, flip-angle=8°, slice thickness=1.2mm, resolution=256x256mm, FOV=26mm. ADNI-GO: Sagittal 3D-IR-SPGR, 8-channel coil, TR=400ms, TE=min full, flip-angle=11°, slice thickness=1.2mm, resolution=256x256mm, FOV=26mm. Images were pre-processed and analysed using SPM8.

Results: Correlation and percentage differences for each tissue type between ADNI-R and ADNI-GO were as follows:[(GM R^2=0.78, ADNI-R 4.55% < ADNI GO) (WM R^2= 0.85, ADNI-R 3.41% > ADNI-GO)(CSF R^2=0.81, ADNI-R 0.34% > ADNI-GO)]. ADNI GO: widespread increases in GM most notably in the cerebellum and pre-central gyrus, and localised decreases along the midline and temporal lobes. ADNI-related: widespread increases in WM, particularly in the cerebellum and pre-central gyrus, and localised decreases in the temporal gyrus.

Conclusions: A widespread increase in GM and localised decrease in WM in ADNI-GO compared to ADNI-R protocols suggest that tissue classification is not equal. Volumetric differences also differ between protocols in the following order of magnitude GM > CSF > WM. This has implications for studies aiming to differentiate groups based on GM differences.

Keywords:
ADNI-related, ADNI GO, MRI, Grey Matter (GM), White Matter (WM), Cerebral Spinal Fluid (CSF)

P26

FRONTOTEMPORAL DEMENTIA AND ALZHEIMER'S DISEASE: HIPPOCAMPAL VOLUMETRY, TENSOR-BASED MORPHOMETRY AND VOXEL-BASED MORPHOMETRY STUDY

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Rationale: MRI is an important clinical tool for diagnosing dementia diseases such as Frontemporal Dementia (FTD). However, there is a need of finding a more accurate and standardized method. The study aimed to compare FTD with Alzheimer's Disease (AD) and Mild Cognitive Impairment (MCI) stages using automatic MRI analysis methods Hippocampal Volumetry (HV), Tensor-based Morphometry (TBM) and Voxel-based Morphometry (VBM), in specific regions of interest in order to find the highest accuracy.

Methods: Thirty-seven patients with FTD, 46 patients with AD, 26 control subjects (C), 16 patients with progressive MCI (P-MCI) and 48 patients with stable-MCI (S-MCI) were included in the HV, TBM, and VBM analyses. We calculated the Correct Classification Accuracy (CCR), sensitivity (SS) and specificity (SP) between the study groups.

Results: We found significant results differentiating FTD from C with HV (hippocampus left side) (CCR=0.826; SS=0.834; SP=0.823), with TBM (hippocampus and amygdala) (CCR=0.828; SS=0.962 SP=0.724), and with VBM (all the regions studied, especially in hippocampus and amygdala) (CCR=0.859; SS=0.963; SP=0,784). The VBM achieved the highest accuracy in differentiating FTD and AD (CCR=0.737; SS=0.776; SP=0.698). The highest level of accuracy differentiating FTD and AD was obtained with lateral ventricle, frontal horn, central part and occipital horn (CCR=0.749). Instead HV resulted in low accuracy CCA (0.578) in differentiation of FTD from AD using all features, and TBM (CCR=0.555) as well.

Conclusion: Hippocampal atrophy is present not only in AD but also in FTD. Of the methods used, VBM resulted in highest accuracy in differentiating between FTD and AD.

P27

DETECTING PRODROMAL AD WITH CURRENT GUIDELINES AND COMPUTER ASSISTED PredictAD TOOL

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Rationale: To compare the accuracies of predicting AD conversion by using a decision support system (PredictAD tool) and current guidelines of prodromal AD as identified by combinations of episodic memory impairment of hippocampal type and visual assessment of medial temporal lobe atrophy (MTA) on MRI, and CSF biomarkers.
Methods: Altogether 391 MCI cases were selected from the ADNI cohort. All the cases had baseline cognitive tests, MRI and /or CSF levels of Aβ1-42 and Tau. Using baseline data, the diagnosis of predromal AD was made based on 1) clinical criteria for episodic memory loss of the hippocampal type, 2) visual MTA, 3) positive CSF markers, 4) their combinations, and 5) PredictAD tool. The accuracies of diagnosis were evaluated with the diagnosis at 2 years later.
Results: The PredictAD tool produced the highest overall accuracy in detecting prodromal AD (72%), followed by clinician's diagnosis with assistance of the PredictAD tool (71%), and those who fulfilled the criteria for episodic memory loss of the hippocampal type and abnormal CSF markers (66%). The overall accuracies did not significantly differ among the three diagnoses ($p=0.105$). The diagnosis by Predict tool alone tended to be significant higher than diagnosis by fulfilling both increased Tau and decreased Aβ1-42 ($p=0.05$), and significantly higher than the diagnosis by the visual MTA or other combinations of clinical diagnoses of hippocampal pattern of memory loss and biomarkers ($p\leq0.003$)
Conclusion: The use of the tool produced comparable or higher accuracies than current diagnostic criteria in detecting the converters and non-converters.

P28

^{11}C-PIB UPTAKE IN "HEALTHY AGING" – HOW MUCH IS TYPICAL FOR WHOM?

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Rationale: Our aim was to elucidate which specific attributes contribute to an apparently healthy populations' brain beta-amyloid (Aß) accumulation, and whether there is interplay between those factors.

Methods: We conducted a cross-sectional ^{11}C-PIB-PET study with 64 cognitively so-far healthy subjects of different ages (54-89 years). In addition to PET, they underwent MRI, neuropsychological testing and apoE sequencing. The explored risk factors' effects on ^{11}C-PIB uptake and the factors' possible interactions were studied with a statistical general linear model as well as with Statistical Parametric Mapping.

Results: The effects of age (p=0.000), apoEε4 carrier status (p=0.000) and sex (p=0.001) on cortical ^{11}C-PIB uptake were all significant. No interactions between the factors were found. The global ^{11}C-PIB score increased by 0.01 with every year of age. The apoEε4 positive subjects had higher ^{11}C-PIB scores than the apoEε4 negative subjects (1.49±0.34 *vs.* 1.29±0.26) and males had higher scores than did females (1.49±0.39 *vs.* 1.29±0.22), irrespective of age. The results of the voxel-based analysis were similar.

Conclusions: The findings of this study underline the effects of age and apoEε4 as independent risk factors for Aß accumulation. The age effect (0.01 ^{11}C-PIB score units / year) seen in this study is in line with previous studies. The more surprising result was that gender had a significant (p=0.001) effect on ^{11}C-PIB uptake, so that men exhibited higher ^{11}C-PIB scores. This difference has not been demonstrated to date, and its possible explanations and implications will be studied further.

P29

NON-ATTENDED AUDITORY EVENT-RELATED POTENTIALS IN MILD COGNITIVE IMPAIRMENT AND ALZHEIMER'S DISEASE

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Rationale: Alzheimer's disease (AD) is a neurodegenerative disorder characterized by a gradual decline in diverse cognitive processes. Event-related potentials (ERPs) provide an objective, non-invasive and cost-effective method for testing cognitive processing and sensory gating.
Methods: Three subject groups were studied: normal controls (NC), patients with mild cognitive impairment (MCI) and patients with incipient AD. While subjects watching a silent attention-capturing movie, tone pips were delivered to both ears in trains of four. The epoched data were averaged separately for the first, second, third and fourth stimulus from each train.
Results: The response evoked by an auditory stimulus includes a positive wave around 50 ms and a negative wave around 100 ms after the stimulus. The P50 component as a response to the first tone appeared consistent in latency and amplitude in NC, MCI and AD. The N100 evoked by the first tone was widened in MCI and AD in comparison to controls. Also the habituation between the first and second tone in P50 and N100 was studied showing no considerable difference between the subject groups. A positive P30 peak emerged more distinct in MCI and AD compared to healthy subjects. The most substantial distinction discovered was MCI and AD having a pronounced P20 component that did not appear among NC.
Conclusions: The study confirms the presence of auditory sensory gating impairment in MCI and AD. The research suggests that auditory ERPs are applicable for individual diagnostics of organic brain diseases and may be used to distinguish early Alzheimer's among MCI.

P30

INCIDENCE OF STROKE IN PERSONS WITH ALZHEIMER'S DISEASE – A NATIONWIDE REGISTER-BASED APPROACH

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Rationale: Stroke increases the risk of Alzheimer's disease (AD), but it is unknown whether AD increases the risk of stroke. We investigated whether non-institutionalised persons with AD have increased risk of stroke and whether there are differences in the incidence of ischemic or haemorrhagic strokes.

Methods: We performed a register-based nested case-control study within a cohort including all community-dwelling persons with verified AD diagnosis in Finland on December 31, 2005 and a single age-, gender and region of residence-matched comparison person without AD for each individual with AD (N=56186, mean age 79.6 (SD 6.9) years, range 42-101 years). Diagnosis of AD is based on prescription reimbursement register and diagnosis of stroke on hospital discharge register. The analyses were restricted to incident strokes (n=3093) occurring between January 1, 2006 and December 31, 2009.

Results: AD was not associated with risk of all strokes or ischemic strokes, but the risk of haemorrhagic strokes was higher among persons with AD (adjusted RR, 95% CI 1.39, 1.14-1.68. When the associations were analysed according to age groups (<75, 75-79, 80-85 and ≥86 years), AD was associated with higher risk of all strokes, regardless of aetiology, in the two youngest age groups, but not in the older groups. Similar associations were observed when the results were categorised according to AD duration.

Conclusions: Persons with AD, especially younger AD patients, have higher risk of strokes, mainly due to increase in bleeds. Our findings accentuate the importance of paying attention to cerebrovascular events also in persons with AD.

P31

APOE4 PREDICTS AMYLOID-β IN CORTICAL BRAIN BIOPSY BUT NOT IDIOPATHIC NORMAL PRESSURE HYDROCEPHALUS

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Rationale: The role of apolipoprotein E (*APOE*) genotype, especially the *APOE4* allele, in Alzheimer's disease (AD) is well-established. However, the predictive value of *APOE* genotype in idiopathic normal pressure hydrocephalus (iNPH) remains elusive. Furthermore, the association of the *APOE4* allele and amyloid-β (Aβ) plaques in cortical brain biopsy was investigated.

Methods: Altogether 202 patients with presumed NPH were evaluated by intraventricular pressure monitoring and frontal cortical biopsy immunostained against Aβ (134 semiquantified by Aβ plaques/mm^2). The 202 patients and 687 cognitively healthy individuals were genotyped for *APOE*. The final clinical diagnoses in a median follow up of 3.9 years were: 113 iNPH (94 shunt-responsive, 16 shunt-non-responsive, 3 not shunted); 36 AD (12 mixed iNPH + AD); 53 others.

Results: The *APOE* genotypes distributed similarly in the 94 shunt-responsive and 16 non-responsive iNPH patients and healthy controls. In multivariate analysis, the *APOE4* allele correlated independently with Aβ plaques in the cortical biopsies (odds ratio 8.7, 95% confidence interval 3.6–20, $p < 0.001$). The *APOE4* allele in presumed NPH predicted later AD as follows: sensitivity 61%; specificity 77%; positive predictive value 37%; negative predictive value 90%.

Conclusion: In presumed NPH patients, *APOE4* associates independently with the presence of Aβ plaques in the frontal cortical biopsy. *APOE4* is not a risk factor for iNPH and does not predict the response to shunt. Our data further support the view that the iNPH syndrome is a distinct dementing disease.

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INFLAMMATION IS ASSOCIATED WITH WORSE COGNITIVE PERFORMANCE IN DIABETICS WITH POOR GLYCEMIC CONTROL: THE ISRAEL DIABETES AND COGNITIVE DECLINE (IDCD) STUDY.

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Rationale: Inflammation has been associated with cognition, and metabolic syndrome has been shown to potentiate its deleterious effect. This study examined the relationship of C-reactive protein (CRP), an inflammatory marker, with cognition, in different levels of long-term HbA1c (the gold standard measure of glycemic control), in 897 non-demented elderly with Type 2 diabetes, who participate in the IDCD.
Methods: Subjects were recruited from the Maccabi Health Services (the second largest HMO in Israel) Diabetes Registry. CRP and cognitive function measures were baseline IDCD assessments. All other measures were the Diabetes Registry average since 1998. We performed partial correlations of three cognitive domains (memory, executive, and psychomotor) with CRP, controlling for age, sex, education, body mass index (BMI), creatinine, cholesterol, and triglycerides, in quartiles of HbA1c.
Results: Subjects averaged 72.9 (SD=4.7) years of age, 13.1 (3.5) years of education, 6.8 (0.78) HbA1c, 28.6 (7.9) body mass index, 1.00 (0.25) creatinine, 180.6 (24.9) cholesterol, and 157.3 (62.9) triglycerides; 41% were women. CRP was associated with executive (r=.14; p=.05) and psychomotor functions (r=.16; p=.02) only in the highest quartile of HbA1c, with poorest glycemic control. Regression analysis showed the linear interaction between CRP and HbA1c quartile approached statistical significance (p=0.06 for executive and p=0.08 for psychomotor functions). CRP and memory were not associated in any quartiles.
Conclusions: Poor glycemic control enhances the effect of inflammation on non-memory cognitive functions in diabetics, suggesting 1) a common underlying mechanism involving both risk factors, and 2) that this relationship contributes a non-Alzheimer's component to diabetes-related dementia.

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MIDLIFE SLEEP CHARACTERISTICS ASSOCIATED WITH LATE LIFE COGNITIVE FUNCTION

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Rationale: Previous studies with limited follow-up times have suggested that sleep-related traits are associated with an increased risk of incident dementia or cognitive decline. We investigated the association between midlife sleep characteristics and late life cognitive function.

Methods: Members of the Older Finnish Twin cohort were sent self-report questionnaires in 1981. These questionnaire data were used in the assessment of sleep characteristics, use of hypnotics and covariates at baseline. Between 1999 and 2007, 2 336 at least 65-year-old twins also participated in a telephone interview assessing cognitive function (mean follow-up 22.1 ± 2.1 years). A linear cognitive score, combining the TELE and TICS scores with a maximum score of 51 was assigned for the participants (mean 38.3 ± 6.1). Linear regression analyses were controlled for age, sex, education, ApoE genotype and follow-up time.

Results: Short (<7 hours/day) and long (>8 hours/day) sleepers had lower cognitive scores as compared to participants sleeping 7-8 hours/day (β -0.84, p=0.01 and β -1.66, p<0.01, respectively). As compared to good sleep quality, poor or rather poor sleep quality was associated with a lower cognitive score (β -1.00, p=0.01). Also, the use of hypnotics on 60 or more days per year was associated with poorer cognitive function (β -1.92, p<0.01). Snoring or insufficient sleep were not associated with cognitive function.

Conclusions: This is the first study indicating that midlife sleep length, sleep quality and use of hypnotics are associated with late life cognitive function. Further confirmation is needed, but these factors may emerge as new risk factors for cognitive impairment.

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MIDLIFE HOPELESSNESS AND WHITE MATTER LESIONS TWO DECADES LATER: A POPULATION-BASED STUDY

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Background: Hopelessness has been associated with increased cardiovascular disease mortality and morbidity, subclinical atherosclerosis and metabolic syndrome. This study investigates the relation between midlife hopelessness and white matter lesions (WMLs) 20 years later in a Finnish population of both men and women.
Methods: Participants of the Cardiovascular Risk Factors, Aging and Dementia (CAIDE) study in Finland were derived from random, population-based samples previously surveyed in 1972, 1977, 1982 or 1987. In 1998, 1449 (73%) individuals aged 65-79 years participated in the re-examination. A subgroup (n=112, including 39 dementia cases, 31 mild cognitive impairment (MCI) cases and 42 controls) underwent 1.5T MRI scanning at re-examination, and WMLs were assessed from FLAIR-images using a semi-quantitative visual rating scale. Hopelessness was measured by 2 questionnaire items (expectations about future and reaching goals).
Results: Subjects with increased hopelessness had a significantly higher risk of developing more severe WMLs two decades later. OR (95% CI) was 4.35 (1.36-13.46) in ordinal regression analyses adjusted for age, sex education, follow-up time, presence of the APOEε4 allele, systolic blood pressure, BMI, history of stroke, heart infarct, smoking and level of midlife leisure physical activity.
Conclusions: Higher levels of hopelessness at midlife seem to be related to more severe WMLs later in life. Since WMLs may contribute to late-life cognitive impairment, lifestyle management of midlife vascular risk factors (which also increase the risk of dementia and cognitive impairment) may have better effects if people´s expectations are more thoroughly discussed.

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FEELINGS OF HOPELESSNESS IN MIDLIFE AND COGNITIVE HEALTH IN LATER LIFE

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Rationale: Although an association between depressive feelings and dementia has been established previously, the nature of this relation remains unclear. Establishing causality has been complicated by the typical use of a short follow-up and aged participants already at baseline. The aim with this study was to investigate the association between feelings of hopelessness in midlife and cognitive impairment in later life.

Methods: From a representative population in Eastern Finland, originally investigated between 1972-1987, a random sample of 2000 survivors was invited for re-examination in 1998, averagely 21 years later. The mean age of the 1449 persons who accepted the invitation was 50.4 (range 39-64) at baseline and 71.3 years (range 65-80) at follow-up. Baseline scores of hopelessness were related to cognitive status at follow-up, mainly through logistic regression. In addition, we analysed differences in hopelessness scores between baseline and follow-up within the different outcome groups.

Results: Participants with high levels of hopelessness at midlife had more than a doubled risk of cognitive impairment in later life as expressed by an odds ratio of 2.24 (1.4-3.6), even higher specifically for Alzheimer's disease. Persons with high levels of hopelessness at midlife and who in addition carried the apolipoprotein allele 4 (APOEε4) had a highly elevated risk of Alzheimer's disease. There were no significant differences in levels of hopelessness between baseline and follow-up within any of the outcome groups.

Conclusions: Carrying feelings of hopelessness in midlife may have long-term implications for cognitive health in later life.

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POOR SELF-RATED PHYSICAL FITNESS IN MIDLIFE PREDICTS DEMENTIA IN OLD AGE

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Rationale: Physical inactivity and cardiovascular diseases, which are known risk factors for cognitive decline, correlate with poor self-rated fitness. This study aims to investigate, whether perceived physical fitness in midlife is associated with subsequent dementia.

Methods: Participants of the Cardiovascular Risk Factors, Aging and Dementia (CAIDE) study were derived from random, population-based samples previously studied in a survey in 1972, 1977, 1982 or 1987. After an average follow-up of 21 years, 2000 survivors aged 65 to 79 were invited for a first re-examination in 1998 and for a second re-examination in 2005-2008. Altogether 1511 individuals (76 %) participated. Multivariate logistic regression models were used to assess the association between midlife self-rated fitness and late-life dementia.

Results: During an average follow-up of 26±6.3 years dementia was diagnosed in 123 participants. Perceived poor physical fitness in midlife increased the risk of subsequent dementia two-fold when compared to persons with good perceived physical fitness (OR 2.1, 95% CI 1.0-4.5). The association was more marked in *APOE 4* non-carriers (OR 5.0, 95% CI 1.6-15.4), but was absent in carriers (OR 1.0, 95% CI 0.3-2.9).

Conclusions: Persons without strong genetic susceptibility for dementia, but who rate their physical fitness in midlife as poor may be at increased risk of developing cognitive deficits. Therefore perceived poor physical functioning could be considered an early warning sign of cognitive decline in old age and preventive measures should be considered in this group.

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CARDIORESPIRATORY FITNESS, MUSCLE STRENGTH AND COGNITION IN INDIVIDUALS 60-75 YEARS OF AGE LIVING IN KUOPIO

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Rationale: Cardiorespiratory fitness is considered to be beneficial to the brain functions. However, the role of muscle strength is still unconfirmed. The aim of this cross-sectional study was to examine the association of cardiorespiratory fitness and muscle strength with cognition.

Methods: The study included baseline data for 125 participants in the Finnish multicenter intervention study, FINGER. Men and women recruited in were 60-75 years of age with increased risk of dementia based on dementia risk score and cognitive performance. Cognitive function was assessed using MMSE, CERAD-word list memory task, LDST and TMT parts A and B. Cardiorespiratory fitness was assessed as maximal oxygen uptake (VO_{2max}). Muscle strength of eight muscle groups was measured with 4 RM-test. Statistical associations were examined with correlation coefficients.

Results: VO_{2max} was directly associated with LDST (r=0,216, p=0,015) and inversely with TMT A (r=-0,204, p=0,022), TMT B (r=-0,295, p=0,002) and TMT B–TMT A (r=-0,283, p=0,003). Muscle strength in knee curl was inversely associated with TMT part A (r=-0,271, p=0,040) as well as strength of thigh and buttock muscles with TMT part B (r=-0,292, p=0,037). Strength of thigh and buttock muscles and pectoral muscles was inversely associated with TMT B-TMT A (r=-0,299, p=0,033) and (r=-0,290, p=0,043), respectively.

Conclusions: The results suggest that cardiorespiratory fitness is positively associated with cognitive function, especially with visuomotoric performance, which demands flexible executive functioning. Neither muscle strength nor maximal oxygen uptake was associated with memory functions. The role of cardiorespiratory fitness and muscle strength on cognition will be further studied including the measurements with MRI.

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SUITABILITY OF CERAD-NB TOTAL SCORE IN THE FOLLOW-UP OF COGNITION IN PATIENTS WITH ALZHEIMER'S DISEASE: KUOPIO ALSOVA STUDY

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Rationale: The Consortium to Establish a Registry for Alzheimer's Disease Neuropsychological Battery (CERAD-NB) is a widely used measure of cognition in Alzheimer's disease (AD) patients. Further studies to validate CERAD-NB total score in monitoring the progression of AD are needed. The aim of the study was to analyze the progression of AD in early diagnosed medicated patients and relationships between cognition, neuropsychiatric symptoms and activities of daily living (ADL) during a follow-up.
Methods: We analyzed the three-year follow-up data of 125 patients with very mild or mild (CDR = 0.5 or 1,0) AD at baseline who were participating in a prospective AD follow-up study (ALSOVA). CERAD-NB total score was used to evaluate cognitive performance, NPI to evaluate neuropsychiatric symptoms and ADSC-ADL in the estimation of ADL.
Results: Cognition and ADL deteriorated, and neuropsychiatric symptoms and severity of dementia increased annually. Progression of AD seemed to accelerate two years after the diagnosis. ADL deteriorated at a slower rate in patients with very mild AD at baseline. The CERAD-NB total correlated well with other cognitive or global measures, but not with NPI.
Conclusions: Our results suggest that the CERAD-NB total is a promising candidate as a follow-up tool to measure global cognition for AD trials. Difference in the deterioration of ADL between patients with very mild or mild AD at baseline emphasizes the importance of early diagnosis. Not only measurement of cognition but especially assessment of ADL and neuropsychiatric symptoms is crucial at the diagnostic visit and in the follow-up.

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CERAD NEUROPSYCHOLOGICAL COMPOSITE SCORES IN PREDICTING PROGRESSION FROM MCI TO ALZHEIMER'S DISEASE – A PROSPECTIVE AddNeuroMed STUDY

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Rationale: The Consortium to Establish a Registry for Alzheimer´s disease Neuropsychological Battery (CERAD-NB) subtests have been found to be sensitive in detecting mild cognitive impairment (MCI) and Alzheimer's disease (AD) in several populations, however, composite scores for the test battery have been studied limitedly. Very little is known about the value of the CERAD composite scores in detecting subjects progressing from MCI to AD.

Methods: We analysed baseline data of 201 subjects with diagnosis of MCI and 212 healthy controls of the prospective multinational AddNeuroMed study. A total of 46 MCI subjects progressed to AD (PMCI) and 155 remained stable (SMCI) at the 1-year follow-up. In addition to two previously described CERAD total scores, a raw score based Memory Total Score and a percentage based Memory Index were calculated. Receiver Operating Characteristic analysis with Area Under the Curve (AUC) was used to evaluate the discrimination accuracy and to produce the optimal cut-off values for different scores.

Results: The Memory Total Score was the most accurate in differentiating PMCI subjects from controls at baseline with optimal cut-off point 28/41 yielding 89.6% sensitivity and 82.6% specificity (AUC=0.913). Global CERAD total scores (AUC=0.912-0.908) were also superior to any CERAD subtests or MMSE (AUC=0.871). Memory Index and Memory Total Score (AUC=0.743-0.739) were the most accurate measures in discriminating PMCI and SMCI subjects.

Conclusions: All composite scores increased the accuracy of CERAD-NB in differentiating PMCI subjects from the controls. Additionally, new memory total scores seem to be applicable in predicting conversion from MCI to AD.

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SUBJECTIVE COGNITIVE COMPLAINTS AND MOOD IN MILD COGNITIVE IMPAIRMENT DIAGNOSIS

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Rationale: Mild Cognitive Impairment (MCI) is a transitional condition between normal aging and dementia and is considered to be prodromal for dementia. One of the diagnostic features of MCI are subjective cognitive complaints. The aim of the study is to describe accurately profile of cognitive functioning of subjects considered having Mild Cognitive Impairment in stable clinical conditions comparing performance in various cognitive tasks with subjective cognitive complaints and their mood.
Methods: 34 subjects with MCI, 25 women, 9 men, from 54 to 82 years old, mean age 68 were assessed for: memory, attention, visuospatial and executive functions (MMSE, Clock Drawing Test, Stroop Task, Verbal Fluency Tasks, Word List Learning and Recall and Digit Span WAIS-R) and screened for anxiety and depression symptoms (Hospital Anxiety and Depression Scale).
Results: Subjective complaints on memory problems did not correlate significantly with any of cognitive tests results. Subjects who reported memory complaints obtained higher mean score on anxiety and depression scales. Nonetheless differences were not statistically significant. These are preliminary results.
Discussion: Subjective cognitive complaints do not necessarily indicate objective impairment of specific cognitive function. Anxiety and depression symptoms may influence self-evaluation of cognitive agility.

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EVALUATING THE DISEASE STATE INDEX AND FINGERPRINT FOR THE CONVERSION FROM MILD COGNITIVE IMPAIRMENT TO ALZHEIMER'S DISEASE IN THE DESCRIPA COHORT

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Rationale: The Disease state index (DSI) is calculated by comparing various test data from a patient to a large group of subjects with or without the disease and determining a value ranging from 0 to 1, depicting which group it is more similar to. The Disease state fingerprint presents DSI data in a visual form enabling a clinician to quickly evaluate the patient's status.

Methods: We investigated how well the DSI can predict the conversion to AD-type dementia for different MCI groups in the DESCRIPA cohort. DESCRIPA is a multicentre study of the European Alzheimer's Disease Consortium, in which non-demented patients with cognitive complaints were followed for 2–3 years. The subjects were divided in groups based on neuropsychological tests. If no impairments were found in neuropsychological tests, the patients were classified as having subjective cognitive impairment (SCI, N=254). Patients with memory impairment were classified as amnestic MCI (aMCI, N=388) and those with impairments in other categories as non-amnestic MCI (naMCI, N=220). In addition to the neuropsychological data, *APOE* gene information, cerebrospinal fluid measurements and computational MRI analysis were available for some subjects.

Results: The Disease state index classifies the patients as stable MCI and progressive MCI with an accuracy of 0.73 for all, 0.68 for aMCI and 0.70 for naMCI patients. However the sensitivity in naMCI is poor making predictions unreliable for this group.

Conclusions: The DSI is effective in predicting conversions from MCI to AD in the DESCRIPA cohort, giving valuable information of the progression of the disease.

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DIET AND COGNITION IN THE FINNISH DIABETES PREVENTION STUDY

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Rationale: Studies suggest an association between diabetes and risk of dementia or cognitive impairment. The Finnish Diabetes Prevention Study (DPS) showed that type 2 diabetes risk can be decreased by 58% with 4-year lifestyle intervention. Hypothetically, diabetes prevention might also prevent cognitive impairment. Our aim was to compare cognitive performance between the former intervention and control groups of the DPS and also investigate associations between cognition and dietary intervention goals.

Methods: CERAD Neuropsychological Battery was performed to 332 DPS participants (64%; mean age 68 y) 13 years after the baseline. Nutrient intakes calculated from food diaries were analysed as achievement of the DPS dietary goals: a) fat intake < 30 E% b) saturated fat (SFA) < 10 E% c) dietary fibre $\geq$15g/1000 kcal.

Results: There were no differences in cognitive performance between the former intervention and control groups. However, participants achieving SFA or fibre goal had higher MMSE scores (p=0.02 and 0.04, respectively) and those reaching fat or SFA goal had better Verbal Performance (p=0.01 and 0.05, respectively). ApoE4 modified the results for Word List Task: achieving SFA goal or all three goals (compared to none) resulted lower scores among apoE4 carriers (p=0.05 and 0.03, respectively) but higher among non-carriers (p=0.02 and 0.01, respectively).

Conclusions: No difference was detected between the groups, possibly because of relatively young age and good cognition of the participants. Achieving dietary goals was associated with better cognitive performance, with the exception of Word List Task among ApoE4 carriers. Interpretation of these results demands further study.

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PLASMA NUTRIENT STATUS OF ALZHEIMER'S DISEASE PATIENTS COMPARED TO COGNITIVE INTACT ELDERLY CONTROLS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Rationale: Alzheimer's disease (AD) patients are at risk of nutritional insufficiencies due to physiological and psychological factors. Since several nutrients are known to influence molecular mechanisms that maintain mental functions, alterations in their levels may have an important impact on AD outcome. To our knowledge, we here provide the first systematic meta-analysis that compares plasma levels of vitamins, minerals, trace elements, and fatty acids in AD patients to those in cognitive intact elderly controls.
Methods: The literature published after 1990 in Cochrane Central Register of Controlled Trials, Medline, and Embase electronic databases was systematically analyzed using the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) (Moher et al. 2009). We retrieved 3080 publications of which 78 met all inclusion criteria.
Results: Significant lower plasma levels of vitamin A ($p=0.0106$), C ($p=0.0250$), E ($p=0.0003$), folate ($p=0.0000$), vitamin B12 ($p=0.0191$), calcium ($p=0.0168$), and zinc ($p=0.0328$) were found in AD patients compared to controls using the random effects mixed model (Sheu et al. 2001). Also, significant lower contents of docosahexaenoic acid (DHA) ($p = 0.0347$) and eicosapentaenoic acid (EPA) ($p = 0.0353$) were found in plasma phospholipids, and of EPA in cholesterylesters ($p = 0.0467$) of AD patients versus controls. No significant differences were observed for plasma levels of vitamin D, copper, iron, magnesium, and selenium; and insufficient publications were retrieved for manganese, vitamin B1, and B6 to perform the meta-analysis.
Conclusions: The overall lower plasma nutrient levels observed indicate that AD is accompanied by specific nutritional requirements.

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THE LipiDiDiet STUDY: RATIONALE AND STUDY DESIGN

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Rationale: Scientific evidence indicates a clear role of nutrition in the development and progression of Alzheimer's disease (AD). Freund-Levi et al. (2006) showed an effect of n-3 fatty acid supplementation on delayed word recall and attention in a subgroup of very mild AD (MMSE >27). More recently, the multi-nutrient drink Souvenaid (containing Fortasyn Connect, a specific combination of nutrients) was tested in a proof-of-concept study in 212 drug naive mild AD subjects and demonstrated improved memory performance (Scheltens et al., 2010).

Methods: To investigate the effects of Souvenaid in elderly who are at high risk of developing AD, the EU-funded[*] 'LipiDiDiet' study started in 2009. The LipiDiDiet study is a 24-month, randomised, controlled, double-blind, parallel-group, study in 300 prodromal AD subjects (according to criteria of Dubois et al., 2007). Subjects are randomly allocated to either active or control product.

Results: Primary outcome measure is the overall performance on a modified version of the Neuropsychological Test Battery (NTB; Harrison et al., 2007). Secondary outcome measures include progression to AD, cognitive performance (ADAS-cog and MMSE), functional abilities (ADCS-ADL), depression (MADRS), MRI atrophy rate, plasma and CSF biomarkers, safety and tolerance and nutritional parameters.

Conclusions: The major study parameters are assessed at baseline, and after 6, 12, and 24 months of intervention.

[*]Funded by the EU FP7 project LipiDiDiet, Grant Agreement N°211696. Souvenaid and Fortasyn are registered trademarks of N.V. Nutricia.

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THE SOUVENAID® CLINICAL TRIAL PROGRAM FOR ALZHEIMER'S DISEASE

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Rationale: The medical food Souvenaid®, containing the specific nutrient combination Fortasyn™ Connect[*], is designed to improve synapse formation and function in patients with Alzheimer's disease (AD). The nutrients in Fortasyn Connect are precursors and cofactors for the formation of neuronal membranes, and increasing their dietary intake can promote synthesis of new brain synapses. The proof-of-concept Souvenir I study demonstrated that 12-week use of Souvenaid improves memory performance in drug-naïve mild AD patients (MMSE 20-26) (Scheltens 2010) and secondary analysis suggested a possible beneficial effect on cognition in patients with worse baseline cognitive performance (ADAS-cog) (Kamphuis 2011).
Methods: To confirm and extend these results, additional randomized controlled double-blind trials with Souvenaid were designed within the Souvenaid Clinical Trial Program: 1) S-Connect: 24-week study investigating the effects on cognitive performance (ADAS-cog) in mild-to-moderate AD patients (MMSE 14-24) using AD medication; 2) Souvenir II: 24-week study investigating the effects on memory performance (memory domain of Neuropsychological Test Battery (NTB)) in drug-naïve mild AD patients (MMSE=20); 3) Souvenir II open-label-extension (OLE): 24-week open-label study aiming to collect long-term safety and compliance data in patients completing Souvenir II; 4) LipiDiDiet[#]: 24-month study investigating the effects on memory performance (modified NTB) in 300 prodromal AD patients (Dubois 2007); 5) Mode of Action of Souvenaid: studies exploring EEG and MEG in Souvenir II and MRS and FDG-PET in future studies.
Results: In Souvenir II, Souvenaid significantly improved memory performance (NTB memory domain) during 24 weeks in drug-naïve mild AD patients (Scheltens, CtAD 2011), thereby confirming and extending the Souvenir I results, whereas the S-Connect study did not show an effect on cognition in more severely impaired patients using AD medication (Shah, CtAD 2011).
Conclusions: Other studies in drug-naïve mild AD and prodromal AD are ongoing.

[*]*Souvenaid and Fortasyn are registered trademarks of N.V.Nutricia.*
[#]*Funded by the EUFP7 project LipiDiDiet, Grant Agreement N°211696.*

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SUPPORTING SYNAPSE FORMATION AND FUNCTION IN ALZHEIMER'S DISEASE: MECHANISM OF ACTION OF THE SPECIFIC NUTRIENT COMBINATION FORTASYN™ CONNECT

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Rationale: AD patients exhibit significant reductions in synaptic membranes and in numbers of synapses. It is recognized that synaptic loss is the best correlate to the cognitive deficits of AD patients. Synapses and neurites consist of neuronal membranes largely composed of phospholipids. Synthesis of phospholipids depends on the presence of the dietary precursors DHA, UMP and choline. Professor Wurtman and co-workers (MIT) have shown that combined administration of these nutrients increases membrane and dendritic spine formation and improves learning and memory in animal models.
Methods: B-vitamins and phospholipids act as dietary co-factors in the synthesis pathway of neuronal membranes by increasing precursor availability. Rodent studies have shown that nutrients synergistically enhance membrane integrity thereby influencing membrane-dependent processes such as M1 receptor function and APP processing, as shown by reduced Aβ production and plaque burden, as well as Aβ toxicity. Epidemiological studies suggest that low intake of n-3 fatty acids, B-vitamins, and antioxidants increase risk of AD, while other studies suggest that patients with AD have lower plasma levels of these nutrients compared to age-matched controls.
Results: Based on these insights the multi-nutrient mixture Fortasyn™ Connect was developed. The effect of Souvenaid®, a 125 ml drink containing Fortasyn™ Connect, on memory and cognitive performance was recently assessed in a proof-of-concept study, with 212 drug-naïve mild AD patients*. The study showed that Souvenaid given for 12 weeks improves memory.
Conclusions: To confirm and extend these findings, three additional studies were initiated. Two studies were completed in 2011, the other will be completed in 2014.

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THE NOVEL DERIVATIVES OF 1-BENZYL-4-((6-ALKOXY-3-OXOBENZOFURAN-2(3H)-YLIDENE) METHYL) PYRIDINIUM WITH POTENT ANTICHOLINESTERASE ACTIVITY FOR ALZHEIMER'S DISEASE (AD) TREATMENT

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Rationale: Mostly observed in elderly populations, Alzheimer's disease (AD) is considered as a common neurodegenerative disorder. Since the decrease of acetylcholine level in the hippocampus and cortex is one of the most important causes of AD, therefore treating by some of acetylcholinesterase (AChE) inhibitors proved to be useful for AD's symptoms.

Methods: A series of novel derivatives of benzofuranone-ylidene-methyl benzylpyridinium were synthesized as acetylcholinesterase inhibitors. The ^{1}H-NMR spectra, mass spectroscopy (MS) spectra and melting points of all compounds were determined. Reaction progress and product mixtures were routinely checked by thin-layer chromatography (TLC) and column chromatography. IR spectra and elemental microanalyses were carried out for C, H, and N. The anticholinesterase activity of synthesized compounds was measured using colorimetric Ellman's method.

Results and conclusions: It was revealed that some synthesized compounds exhibited significantly higher anticholinesterase activity compared to the donepezil hydrochloride (IC50 = 28 ± 6.62 nM), among them compound 6b was the most active compound (IC50 = 10 ± 6.87 nM). To gain insight into the molecular determinants those modulate the inhibitory activity of these compounds, molecular docking simulations for 6b to TcAChE were performed using the autodock vina program based on the X-ray crystal structure of TcAChE-E2020 complex.6b has a nice fit in the active-site gorge of AChE similar to donepezil, binding to the central subsite and the peripheral anionic site simultaneously.

Keywords:
Alzheimer's disease; Molecular docking simulations; Benzofuranone; Benzylpyridinium; Cholinesterase inhibitor

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ELECTROMAGNETIC FIELD EXPOSURE AND ALZHEIMER'S DISEASE

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Rationale: In certain occupations, there is an increased risk of Alzheimer's disease (AD), like locomotive drivers, welders, seamstresses, IT employees etc. (Garcia *et al*. 2008). People who live close to power lines have an increased AD risk (Huss *et al*. 2008), though there is a small number of epidemiological studies focusing on AD. We have carried out an extensive questionnaire among subjects (N=255) reporting electromagnetic sensitivity (Hagström 2012, forthcoming).
Several mechanisms are reported in the literature:
1. Amyloid-β (Aβ) increases in brain cells because of Blood Brain Barrier (BBB)-leakage. Electromagnetic fields (EMF), especially pulsed microwave radiation affect BBB, but this effect is not linear and the greatest power densities do not make the BBB leak (Frey 1974, Salford *et al.* 2007).
2. Increased peripheral or brain production of Aβ as a result of magnetic field exposure cause voltage-gated calcium ion channels to be open longer than normal. This results in abnormally high intracellular levels of calcium ions, which in turn results in the production of Aβ and that is quickly secreted into the blood and is then transported through the BBB perhaps best chaperoned by the 4 isoform of apolipoprotein E (apoE) (Davanipour and Sobel, 2009).
3. Positron emission tomographic (PET) studies of cerebral glucose metabolism have shown high diagnostic specificity in distinguishing among the degenerative dementias and differentiating between AD and normal aging (Smith *et al*., 1992). Volkow *et al.* (2011) have showed through a PET study that 50-minute mobile phone call increases glucose metabolism in the brain. This finding is similar to Huber *et al*. (2002).
4. EMF exposures decrease acetylcholine levels in brain (Modak *et al*. 1981).
5. EMFs affect pineal gland and decrease its melatonin production (which may increase the risk of AD) (Srinivasan *et al.* 2006).
Conclusion: There is substantial evidence that electromagnetic field exposure is related to Alzheimer's disease. However, the mechanism is debated and similarly a proper risk-group identification is under discussion. Based on our findings, high EMF exposure may increase AD risk in those being naturally sensitive to electromagnetic fields.

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CORTISOL, MEMORY AND HIPPOCAMPAL VOLUME IN OLDER AND YOUNG ADULTS: THE ROLE OF STRESSFUL TESTING ENVIRONMENTS

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Rationale: Healthy older adults show impaired memory performance compared to young adults. This association may be related to hippocampal volume (HV). Elevated stress hormones (cortisol) impair cognition. Yet, it is unknown whether testing-environments themselves might function as stressors.
Goals: In testing environments manipulated to induce higher or lower distress for each age group A) to compare memory performance of older and young adults, B) to assess whether HV is associated with memory and cortisol.
Methods: 32 healthy older adults and 28 young adults were each tested in two environments: 1) Environment (A) – stressful for older adults, non-stressful for young: on university grounds, PM-testing by a young student; 2) Environment (B) – non-stressful familiar environment for older adults, stressful for young: AM-testing by an older adult. Declarative memory and cortisol were assessed in both environments. MRI scans were performed.
Results: 1) In the non-stressful environment for older adults, their forgetting rate is equivalent to that of young adults. However, in the stressful environment, they are more forgetful. 2) Among older adults, HV is associated with memory only in the stressful environment. For older and young adults, HV is significantly correlated with cortisol when tested in stressful environments for their respective age groups.
Conclusion: Only in the non-stressful environment, the forgetting rate of older adults is equivalent to young adults, their HV is associated with memory and cortisol. The latter association (HV-cortisol) was also found in young adults. These findings highlight the importance of stressful testing-environments, as older adults may be more susceptible to stress-induced memory impairments.

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DOES THE EARLY BIRD *REALLY* CATCH THE WORM?: OLDER ADULTS' PREFERENCE FOR TESTING TIME AFFECTS CORTISOL LEVELS AND MEMORY PERFORMANCE

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Rationale: Older adults generally rate themselves as 'morning-types'. Indeed, older adults demonstrate better memory performance in the morning compared to the afternoon. Because circadian variations in stress hormones (cortisol) are also known to influence cognitive abilities, the aims of this study were to: (1) assess whether preferences for testing time (morning/afternoon) are associated with cortisol levels; and (2) evaluate the association between cortisol and memory, with sleep entered as a modulating variable.
Methods: Thirty-two healthy older adults were each tested in two environments: (1) Unfavourable-PM-environment: on university grounds, testing by a young student; (2) Favourable-AM-environment: testing by an older adult. Declarative memory and cortisol were assessed in both environments. Validated questionnaires on sleep and chronotype were administered.
Results: 1) Among older adults tested in PM hours, those with a preference for earlier testing time (8:00 – 10:00 AM) had higher cortisol levels than those with a preference for later testing time (11:00 AM – 1:00 PM). Cortisol levels were significantly correlated to memory performance only during the Unfavourable-PM-environment. After covarying for sleep duration , significance was attenuated.
Conclusion: Older adults who are mis-matched with their preferred testing time experience heightened distress. While elevated cortisol is associated with worse memory performance, this association is modulated by sleep duration. Our findings highlight the importance of testing older adults during their preferred testing time to avoid the confounding effects of circadian processes that can obscure interpretations.

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GENDER DIFFERENCES AND TIME TRENDS IN DEMENTIA SPOUSAL CAREGIVERS' BURDEN

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Rationale: Caregivers' high burden has been investigated in a number of dementia studies. However, we lack large scale studies investigating the gender differences and time trends in continuous caregiving concerning burden affecting caregivers' wellbeing. The aim of this study is to compare the burden of male and female spousal caregivers of persons with dementia. In addition, we studied the effect of time and progression of dementia on these findings during a one-year follow-up.

Methods: We used data from our two previous intervention trials using the same measure (Zarit burden scale) in a one-year follow-up. The interventions of original trials (1) case manager trial, 2) exercise intervention trial) did not have effect on caregivers' burden. Therefore, this material is used to investigate the time trends of these measures without taking into account the randomization group. Altogether 335 couples were investigated, 128 male and 207 female caregivers. CDR, MMSE and Zarit burden scale were used to measure dementia stage, cognition and burden, respectively.

Results: At the baseline the caregivers' mean age was 77 years. The male caregivers' spouses with dementia were on more severe stage according to CDR than female caregivers' spouses ($p=0.048$). The mean MMSE among male caregivers' spouses was 14.0 (SD 7.1) whereas the respective figure among the female caregivers' spouses was 17.7 (SD 6.2) ($p<0.001$). However, the male caregivers experienced less burden than the females according to the Zarit burden scale (31.5 vs. 37.5, $p<0.001$). In logistic regression analysis adjusted for age and CDR, the male gender was protective against high burden (Zarit>40 points) (OR 0.38; 95%CI 0.23 to 0.66). The burden of both genders decreased during the follow up year: at 12 months the mean Zarit among males was 27.3 vs. among females 35.9.

Conclusion: Males experience significantly less burden while taking care of their spouses with dementia.

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PREVENTION AND EARLY DIAGNOSIS OF MEMORY DISORDERS IN THE TAMPERE REGION (MEVA)

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Rationale: MEVA-project, administered by Pirkanmaan Muistiyhdistys ry, aims at prevention of proceeding memory disorders in the Tampere region. The objective is to promote early diagnosis of memory disorders and add common knowledge about promoting brain health and preventing memory disorders. The actors of the project are the units of health centres and occupational health centres.
Methods: With the help of a risk test for memory disorders, it is aspired to find middle-aged and older clients of health care system with an increased risk of memory disorder, and to direct them towards the needed changes in life style. Personal and group counseling are used as an intervention. People are supported to change life habits independently.
Results: The object is to create a permanent procedure in the primary health care and the units of occupational health within the project period (2011-2014) in order to promote and support the prevention and early diagnosis of memory disorders. Project supports the organizations of the actors involved in developing the needed functions.
Conclusions: Memory disorders constitute a considerable public health problem. Even though these disorders cannot be healed as such, the onset of the illness can be delayed. The risk of memory disorder can be reduced by healthy life style and fostering brain health.

Notes

Presenting author index

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Käyttöaiheet: Lääkevalmiste on tarkoitettu kohtalaista tai vaikeaa Alzheimerin tautia sairastavien potilaiden hoitoon. **Annostus ja antotapa:** Memantiini annostellaan kerran vuorokaudessa. Enintään 20 mg vuorokaudessa. Ylläpitoannokseen on siirryttävä vaiheittain: hoito aloitetaan annoksella 5 mg vuorokaudessa ensimmäisen viikon aikana. Toisella viikolla suositellaan 10 mg annosta vuorokaudessa ja kolmannella viikolla 15 mg annosta vuorokaudessa. Hoitoa voidaan jatkaa neljännestä viikosta alkaen suositellulla ylläpitoannoksella 20 mg vuorokaudessa. Tabletit tai oraaliliuos voidaan ottaa ruokailun yhteydessä tai erikseen. Vanhukset: Kliinisiin tutkimuksiin perustuva annostussuositus yli 65-vuotiaiden potilaiden osalta on 20 mg vuorokaudessa edellä kuvatulla tavalla. **Vasta-aiheet:** Yliherkkyys vaikuttavalle aineelle tai apuaineille. **Varoitukset ja käyttöön liittyvät varotoimet:** Hoitoa ei suositella potilaille, joilla on vaikea maksan vajaatoiminta. Varovaisuutta suositellaan hoidettaessa epilepsiasta kärsiviä potilaita. Samanaikaista NMDA-antagonistien käyttöä on vältettävä. Jotkin virtsan pH-arvoa nostavat tekijät voivat edellyttää potilaan tarkkaa seurantaa. Useimmissa kliinisissä kokeissa potilaat, joilla on hiljattain ollut sydäninfarkti, kompensoitumaton sydämen vajaatoiminta (NYHA III-IV) tai hallitsematon verenpainetauti, suljettiin pois. Tästä johtuen tällaisia potilaita koskevia tietoja on saatavana vain vähän, ja heitä on seurattava tarkkaan. **Yhteisvaikutukset muiden lääkevalmisteiden kanssa sekä muut yhteisvaikutukset:** L-dopan, dopaminergisten agonistien ja antikolinergien samanaikainen käyttö memantiinin kaltaisten NMDA-antagonistien kanssa saattaa voimistaa niiden vaikutusta. Barbituraattien ja neuroleptien vaikutus voi heikentyä. Memantiinin anto samanaikaisesti kouristuksia ehkäisevien lääkeaineiden, dantroleenin tai baklofeenin kanssa saattaa muuttaa niiden vaikutuksia. Memantiinin ja amantadiinin samanaikaista käyttöä tulisi välttää. Tämä saattaa koskea myös ketamiinia ja dekstrometorfaania. Memantiinin ja fenytoiinin yhdistämisen mahdollisesta vaarasta on julkaistu yksi tapausselostus. Myös muut lääkeaineet kuten simetidiini, ranitidiini, prokainamidi, kinidiini, kiniini ja nikotiini, voivat mahdollisesti aiheuttaa plasmatason kohoamisen vaaran. Mahdollisesti hydroklooritiatsidin (HCT) seerumitaso alenee, kun memantiinia annetaan HCT:n tai HCT-yhdistelmävalmisteen kanssa. Memantiini ei estänyt CYP 1A2-, 2A6-, 2C9-, 2D6-, 2E1-, 3A-isoentsyymejä, flaviinia sisältävää mono-oksigenaasia, epoksidihydrolaasia eikä sulfataatiota in vitro -tutkimuksessa. Protrombiini-ajan tai INR-arvon seuranta on suositeltavaa, jos potilas saa oraalista antikoagulanttihoitoa samanaikaisesti memantiinin kanssa. **Haittavaikutukset:** Kohtalaista ja vaikeaa dementiaa koskevissa kliinisissä kokeissa haittavaikutusten kokonaisilmaantuvuus ei poikennut lumehoidosta, haittavaikutukset olivat tavallisesti lieviä tai kohtalaisia. Useimmin esiintyvät haittavaikutukset: huimaus, päänsärky, ummetus, uneliaisuus ja kohonnut verenpaine. **Ebixa® pakkaukset ja hinnat (VMH sis. ALV 9%) 1.1.2011:** Ebixa-tabletti 10 mg: 30 tabl. 66,98 €, 50 tabl. 107,80 €, 100 tabl. 203,32 €, Ebixa-tabletti 20mg: 28 tabl. 119,95 €, 98 tabl. 381,60 €. Ebixa aloituspakkaus 5 mg+10 mg+15 mg+20 mg: 28 tabl. 77,46 €. Ebixa 5 mg/pumpun painallus oraaliliuos: 50 ml 107,82 €. **Korvattavuus:** Peruskorvattu erillisselvityksen perusteella (307). **Lisätiedot:** Oy H. Lundbeck Ab, puh. (02) 276 5000 tai Pharmaca Fennica. 03/2012 **Viitteet:** 1) Jones RW A Review Comparing the Safety and Tolerability of Memantine with the Acetylcholinesterase Inhibitors. International Journal of Geriatric Psychiatry 2010;25(6):574–553 2) Reisberg B. et al. Memantine in Moderate to Severe Alzheimer's Disease. New England Journal of Medicine, 2003; 348: 1333–1341. 3) Winblad B. et al. Memantine in severe dementia: results of the 9M-Best study (Benefit and Efficacy in Severely Demented Patients During Treatment with Memantine). Int J Geriatric Psychiatry 1999; 14: 135–146. 4) Wimo A. et al. Resource Utilization and Cost Analysis of Memantine in Patients with Moderate to Severe Alzheimer's Disease, Pharmaco-economics 2003; 21(5): 327–340.

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Käyttöaihe: Aikuisille idiopaattisen Parkinsonin taudin oireiden hoitoon yksin (ilman levodopaa) tai yhdessä levodopan kanssa. **Annostus:** Aloitusannos 0,26 mg pramipeksolia (vastaa 0,375 mg pramipeksolisuolaa) kerran vuorokaudessa. Annosta suurennetaan aloitusannoksesta vähitellen joka 5. – 7. päivä. Annos voidaan kaksinkertaistaa viikon välein 1,05 mg:n (vastaa 1,5 mg suolaa) vrk-annokseen saakka. Tarvittaessa vrk-annosta voidaan nostaa 0,52 mg (vastaa 0,75 mg pramipeksolisuolaa) viikottain aina 3,15 mg:n maksimivrk-annokseen saakka (vastaa 4,5 mg pramipeksolisuolaa). On kuitenkin huomattava, että uneliaisuuden esiintymistiheys lisääntyy käytettäessä 1,05 mg pramipeksolisuolaa/päivä suurempia annoksia. Sifrol-tabletteja käyttävät potilaat voivat siirtyä käyttämään Sifrol-depottabletteja yhdessä yössä samalla vuorokausiannoksella. Sifrol-depottabletteihin siirtymisen jälkeen annosta voidaan säätää riippuen potilaan terapeuttisesta vasteesta. Sifrol-depottabletteja ei saa pureskella, jakaa tai murskata. Hoitoa lopetettaessa annosta tulee vähentää asteittain. Munuaisten vajaatoiminnassa annosta on syytä pienentää. **Vasta-aiheet:** Yliherkkyys vaikuttavalle aineelle tai apuaineille. **Varoitukset ja käyttöön liittyvät varotoimet:** Pramipeksolin käytön yhteyteen on liittynyt uneliaisuutta ja äkillistä nukahtamista. Potilaita pitää neuvoa olemaan varovaisia ajaessaan autoa tai käyttäessään koneita sekä varoittaa mahdollisesta pramipeksolin vaikutuksen lisääntymisestä yhdessä rauhoittavien lääkkeiden tai alkoholin kanssa. Parkinsonin tautia sairastavilla potilailla, joita on hoidettu dopamiiniagonisteilla, Sifrol mukaan lukien, on etenkin suuria annoksia käytettäessä ilmoitettu esiintyneen merkkejä sairaalloisesta pelihimosta, lisääntyneestä libidosta, hyperseksuaalisuudesta, ahmimisesta ja pakonomaisesta ostamisesta. Nämä ovat yleensä korjautuneet annoksen pienentämisen tai hoidon lopettamisen jälkeen. Potilaille on kerrottava aistiharhojen, yleensä näköharhojen, esiintymismahdollisuudesta. Pitkälle edenneen Parkinsonin taudin hoidossa yhdistelmähoito levodopan kanssa saattaa aiheuttaa tahattomia pakkoliikkeitä hoidon alussa, kun Sifrol annosta suurennetaan. Jos niitä esiintyy, tulee levodopa-annosta vähentää. Oftalmologisia tutkimuksia suositellaan säännöllisin väliajoin tai jos näkökyvyn heikkenemistä esiintyy. Käytettäessä Sifrolia potilaalla, jolla on vaikea kardiovaskulaarinen sairaus, tulee noudattaa varovaisuutta. Verenpaineen tarkkailua suositellaan erityisesti hoidon alussa, koska posturaalinen hypotensio liittyy yleisenä riskitekijänä dopaminergiseen hoitoon. **Yhteisvaikutukset muiden lääkeaineiden kanssa:** Pramipeksolilla voi olla yhteisvaikutuksia simetidiinin, amantadiinin, meksiletiinin, tsidovudiinin, sisplatiinin, kiniinin ja prokaiiniamidin kanssa. Pramipeksoliannoksen pienentämistä tulee harkita, kun näitä lääkkeitä käytetään samanaikaisesti Sifrolin kanssa. Kun Sifrolia annetaan yhdessä levodopan kanssa, suositellaan levodopa-annoksen pienentämistä ja muiden parkinsonismilääkkeiden annoksen säilyttämistä ennallaan, kun Sifrolin annosta suurennetaan. Antipsykoottisten lääkkeiden käyttöä yhdessä pramipeksolin kanssa tulee välttää. **Raskaus ja imetys:** Sifrol-tabletteja ei pitäisi käyttää raskauden aikana mikäli käyttö ei ole selvästi välttämätöntä. Sifrolia ei tule käyttää imetyksen aikana. **Vaikutus ajokykyyn ja koneiden käyttökykyyn:** Sifrolilla voi olla tuntuva vaikutus ajokykyyn ja koneiden käyttökykyyn. Hallusinaatioita ja uneliaisuutta saattaa ilmetä. Potilaita, joilla esiintyy uneliaisuutta ja/tai äkillistä nukahtamista, pitää neuvoa olemaan ajamatta autoa, kunnes toistuvat oireet ja uneliaisuus katsotaan hävinneiksi. **Haittavaikutukset:** Yleisimmin ilmoitetut haittavaikutukset ovat heitehuimaus, dyskinesia, uneliaisuus, hypotensio, pahoinvointi, päänsärky, epänormaalit unet, heikentyneeseen impulssikontrolliin ja pakko-oireiluun liittyvät käyttäytymisoireet, sekavuustila, aistiharhat, unettomuus, näön heikkeneminen mukaan lukien kahtena näkeminen, näön hämärtyminen ja huonontunut näöntarkkuus, ummetus, oksentelu, uupumus, perifeerinen turvotus ja painon väheneminen mukaan lukien ruokahalun väheneminen. Muut haittavaikutukset ks. PF. **Pakkaukset ja hinnat VMH sis. Alv.** Sifrol depottabletti 0,26 mg (0,375 mg) 30 tabl. 31,32 €, 100 tabl. 90,39 €. Sifrol depottabletti 0,52 mg (0,75 mg) 30 tabl. 56,49 €, 100 tabl. 158,30 €. Sifrol depottabletti 1,05 mg (1,5 mg) 100 tabl. 299,98 €. Sifrol depottabletti 1,57 mg (2,25 mg) 100 tabl. 437,52 €. Sifrol depottabletti 2,1 mg (3 mg) 100 tabl. 573,77 €. Sifrol depottabletti 2,62 mg (3,75 mg) 100 tabl. 702,73 €. Sifrol depottabletti 3,15 mg (4,5 mg) 100 tabl.834,65 €. Reseptilääke. 100 % korvattava Parkinsonin taudin ja siihen verrattavien liikehäiriöiden hoidossa (110). **Lisätiedot:** Pharmaca Fennica tai Boehringer Ingelheim Finland Ky, Tammasaarenkatu 5, 00180 Helsinki, puh. 010 3102 800.

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Lisätiedot: Pharmaca Fennica ja aesculapius.fi

05/2012

Annakaisa Haapasalo (ed.)

6th Kuopio Alzheimer Symposium

On the road to early diagnosis, treatment, and prevention of Alzheimer's disease
Kuopio, Finland, June 14-16, 2012

Program and Abstracts

The 6th Kuopio Alzheimer Symposium is organized by the University of Eastern Finland, Institute of Clinical Medicine – Neurology, the Finnish Alzheimer's Disease Research Society, AlzPoint, and the Doctoral Program in Molecular Medicine. It brings together the current leaders in clinical and basic research for exchanging new ideas on early diagnosis, brain imaging, biomarkers, search for drug targets, prevention, and treatment and care of Alzheimer's disease. The Finnish program of the Memory Day (Muistipäivä) concentrates on the guidelines of good care.

This book contains the program and abstracts of the 6th Kuopio Alzheimer Symposium held in Kuopio, Finland, June 14-16, 2012

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