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The 5th Kuopio Alzheimer Symposium

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June 11-13, 2009

Program
and
Abstracts

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Dear Colleagues and Friends,

You are cordially welcome to participate in the 5th Kuopio Alzheimer Symposium in Kuopio, Finland, June 11-13, 2009.

This series of meetings focuses on different important areas of Alzheimer's disease research. Our goal is to bring scientists and clinicians together and provide a forum for new ideas for future research and subsequently for treatment and prevention options. The first meeting was held on January 28-30, 1999 in freezing cold temperatures. This time we decided to fulfil the wish of many speakers to organize the meeting in summer.

Like in previous meetings we have succeeded in composing an interesting program with top speakers. The program will focus on new exciting data concerning frontal dementias, early diagnosis, symptomatic treatment and emerging disease modifying treatment options including dietary interventions and rehabilitation of dementia. New criteria of Alzheimer's disease will be discussed with the scientists who were participants of the working group formulating these criteria. The value of biomarkers and brain imaging in early diagnosis of Alzheimer's disease will be critically evaluated. Roadmap to prevention of Alzheimer's disease will be a hot topic in years to come and top speakers in Kuopio Alzheimer Symposium will discuss options in prevention as well.

I warmly welcome you to Kuopio to enjoy this exciting scientific meeting, which will also provide you an opportunity to experience the Finnish summer.

Kuopio, June 2009

Hilkka Soininen
Professor, Chairperson of the Organizing Committee

The 5th Kuopio Alzheimer Symposium

Organized by
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Institute of Clinical Medicine, Neurology
University of Kuopio Neuroscience Centre
Nordic Centre of Excellence of Neurodegenerative Diseases
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The 5th Kuopio Alzheimer Symposium

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ORAL PROGRAM

THURSDAY, JUNE 11, 2009

THE 5th KUOPIO ALZHEIMER SYMPOSIUM

OPENING SYMPOSIUM

18:00-18:15	**Welcome addresses** Matti Uusitupa, Rector, University of Kuopio Hilkka Soininen, Chair of the Organizing Committee
	HOT TOPICS IN DEMENTIA RESEARCH **Chairpersons: Niels Prins and Juha Rinne**
18:15-19:00	**The emerging role of oligomers in Alzheimer's disease** Dominic Walsh, University College Dublin, Ireland
19:00-19:45	**Molecular brain imaging** Agneta Nordberg, Karolinska University Hospital, Sweden
20:00-22:00	**Welcome Reception** Microteknia

THE EMERGING ROLE OF OLIGOMERS IN ALZHEIMER'S DISEASE

Dominic M. Walsh
Laboratory for Neurodegenerative Research, Conway Institute, University College Dublin, Republic of Ireland

Background: Growing evidence suggests that non-fibrillar forms of Aβ play an important role in Alzheimer's disease (AD). Here we describe the synaptotoxic properties of SDS-stable Aβ dimers present in certain samples of human CSF and extracts of AD brain.
Methods: Using a sensitive IP/Western blot protocol we detected dimer in ~20% of CSF samples analyzed. Three samples containing monomer alone and six samples containing monomer plus dimer were tested for their effect on hippocampal LTP. Aqueous brain extracts containing Aβ dimers were also tested for their effect on LTP and the performance of trained rats in an avoidance learning task.
Results: CSF samples that contained SDS-stable Aβ dimer caused a robust block of LTP, whereas samples that contained only Aβ monomer had no effect. Moreover, extracts of human brain that contained SDS-stable Aβ dimers blocked LTP and impaired the memory of learned behaviour. Although these data strongly suggested that Aβ dimers were synaptotoxic, there remained the possibility that additional co-factors were also required. To address this possibility, we tested the effect of pure synthetic Aβ 1-40 dimer. This synthetic dimer blocked LTP with a potency at least 20 times greater than freshly dissolved monomer. Initial immunological analysis indicates that the synthetic dimer is distinct from monomer.
Conclusions: These results suggest that Aβ dimers are potent synaptotoxins and may be tractable targets for the development of disease-modifying therapy.

MOLECULAR BRAIN IMAGING

Agneta Nordberg
Karolinska institutet, Division of Alzheimer Neurobiology, Karolinska University Hospital, Stockholm, Sweden

Alzheimer's disease (AD) is a complex disease characterized by a whole cascade of pathological events triggered following the appearance of abnormal amyloid in brain. It is still not yet clear how early the amyloid deposit starts in the course of the disease and what form of amyloid that is most toxic for the brain. The recent rapid development of the molecular imaging techniques allows in vivo imaging not only of brain functional activity such as cerebral blood flow, cerebral glucose metabolism and neurotransmitter activity, and receptor density, but also pathological processes such as amyloid plaques and microglial activation in AD. The mechanism of action present cholinesterase inhibitors have been studied by PET. Several PET amyloid imaging ligands have recently been developed and tested in AD patients. So far PIB is the most explored amyloid ligand studied by PET. High PIB retention is measured in prodromal AD preceding impairment of functional activity like cerebral glucose metabolism, and reduction in cholinergic activity, which are likely to follow the course of cognitive impairment. PIB brain imaging is mainly negative in other forms of dementia including fronto-temporal dementia and Parkinson's disease. A proportion of cognitively normal elderly show high PIB retention in brain. There is great hope that amyloid imaging may help in the early detection of the AD and be used for evaluating new drug therapies including neuroprotective and preventive therapies. Multi-tracer PET studies in subjects at risk of AD open up new possibilities for insight into the complex pathological mechanisms in AD.

FRIDAY, JUNE 12, 2009

MAIN SYMPOSIUM

I NEUROPATHOLOGY OF DEMENTIAS
Chairperson: Agneta Nordberg

08:30-09:00 **Pathologic classification of frontotemporal degeneration**
Tamas Revesz, UCL Institute of Neurology, UK

09:00-09:30 **Correlations between clinical and pathological diagnosis in dementia**
Elisabet Englund, University Hospital Lund, Sweden

09.30–10.00 Coffee break

II PROGNOSIS OF COGNITIVE DECLINE
Chairpersons: Tuula Pirttilä and Pieter Jelle Visser

10:00-10:30 **Preventing cognitive decline: Current status and future directions**
Miia Kivipelto, Karolinska Institutet, Sweden

10:30-11:00 **Alzheimer's disease and cerebrovascular disease - secret partners in cognitive decline**
Timo Erkinjuntti, University of Helsinki, Finland

11:00-11:30 **Improved prognosis of cognitive change in healthy aged and MCI subjects: Is there still a need for placebo control in preventative clinical drug trials?**
René Spiegel, Geriatric University Hospital Base, Switzerland

11.30–12.30 Lunch break

PATHOLOGICAL CLASSIFICATION OF FRONTOTEMPORAL DEGENERATION

Tamas Revesz
Queen Square Brain Bank, UCL Institute of Neurology, Queen Square, London, United Kingdom

Background: Frontotemporal dementia is a clinical term describing progressive overlapping syndromes characterized by behavioural changes, loss of word and object knowledge and aphasia. Frontotemporal lobar degeneration (FTLD) characterised by relatively selective degeneration of frontal and temporal lobes, is the unifying term to describe neuropathological entities underlying these clinical syndromes.
Methods: A recent neuropathological classification of FTLD is based on the presence of specific neuronal (and in some cases also glial) protein inclusions indicating underlying molecular mechanisms.
Results: In a large group of FTLDs the inclusions are composed of the microtubule associated protein tau (FTLD-tau). Among others the entities include Pick's disease, CBD, PSP and AGD. In the majority of the heterogeneous group of tau-negative FTLDs the inclusions are ubiquitin-positive and contain the TAR DNA-binding protein 43 (TDP-43) (FTLD-TDP). Based on the predominant inclusion type (neuritic, neuronal cytoplasmic, neuronal intranuclear) four subtypes of FTLD-TDP have been established and successful attempts have also been made to correlate these with clinical presentation/subtypes. The latest pathological classification of FTLDs also includes rare entities such as FTLD with ubiquitin-positive, but TDP-43-negative inclusions (FTLD-UPS), the neuronal intermediate filament inclusion disease and dementia lacking distinctive histology, in which no inclusions have been identified as yet.
Conclusions: Classification of FTLDs based on the presence of cellular protein inclusions provides a workable framework for future clinicopathological studies and further research aiming to understand the disease mechanisms underlying FTLDs.

CORRELATIONS BETWEEN CLINICAL AND PATHOLOGICAL DIAGNOSIS IN DEMENTIA

E. Englund, H. Brunnström
Dept of Neuropathology, University Hospital, Lund, Sweden

Accurate distinction between dementia subtypes is important for patient care and pharmacological treatment. Clinico-pathological studies contribute to the improvement of dementia diagnostics and continuing systematic comparisons provide valuable feedback for further increasing diagnostic accuracy.
This report describes the concordance between clinical and pathological dementia diagnoses in a recent material from the south of Sweden. Patients with a clinical dementia diagnosis from a specialized unit and later neuropathological (NP) examination performed in Lund 1996 - 2006 were assessed (n=176).
The most frequent NP diagnoses were Alzheimer's disease (AD) in 35%, vascular dementia (VaD) in 15%, frontotemporal lobar degeneration in 13% and mixed AD+VaD in 12%. The clinical and NP diagnoses were in full concordance in 49% of the cases (n=86), while in an additional 14%, the clinical diagnosis corresponded with some but not all structural alterations judged clinically significant.
Among the patients with a clinical AD diagnosis, 64% had pure AD at NP, while altogether 84% included AD with concurrent other significant pathology. The corresponding figures for AD+VaD were 19% and 25%, respectively. The reasons for the discrepancies in dementia diagnosis and the variations in dementia subtype concordance will be discussed, as well as the clinical implications of these findings.
Furthermore, the correlation between cerebrospinal fluid evaluation of tau and amyloid B in a subset of 43 cases subsequently NP analysed will also be presented and related to the results in clinico-pathological concordance.

PREVENTING COGNITIVE DECLINE: CURRENT STATUS AND FUTURE DIRECTIONS

Miia Kivipelto
Ageing Research Center, Karolinska Institutet, Stockholm, Sweden, and Department of Neurology, University of Kuopio, Finland

Background: There is increasing evidence that cognitive impairment is a heterogeneous and multi-factorial condition with several vascular and lifestyle related risk factors.
Objective: This is a brief overview of the present status of cognitive impairment with respect to classifications, diagnostic criteria and their influence on prevention studies. Current modifiable risk factors and prevention trials results are discussed, as well as future directions in planning preventive interventions.
Results: Previous preventive trials with single agents in elderly or already cognitively impaired persons have yielded disappointing results (e.g. hormonal replacement therapy, NSAIDs, vitamin E, cholinesterase inhibitors among persons with MCI). Intervention studies integrating several different approaches have not been done for MCI or AD so far. *The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER)* is the first multi-domain intervention study primarily designed to delay cognitive impairment among high-risk individuals. The 2-year multi-domain intervention will have four main components: i) Nutritional guidance, ii) Physical activity, iii) Cognitive training and social activity, iv) Intensive monitoring and management of vascular risk factors.
Conclusions: A lifelong perspective is needed for managing cognitive impairment. Epidemiological findings indicated that it may be possible to reduce the risk or postpone the onset of dementia by adopting healthy lifestyle options. However, the focus needs to be shifted from the extreme category of dementia to the continuum of cognitive functioning. The ongoing RCTs will clarify to what extent a multi-domain intervention will delay cognitive impairment.

ALZHEIMER'S DISEASE AND CEREBROVASCULAR DISEASE - SECRET PARTNERS IN COGNITIVE DECLINE

Timo Erkinjuntti
Department of Neurology, University of Helsinki, Helsinki, Finland

Alzheimer's disease (AD) as the most frequent progressive memory disease is recognized as a stage-concurrent disorder. AD core pathology has a site specific evolution over time, and AD symptoms and their progression is understood by the location of the lesions; from early AD to more severe stages. The old AD research criteria by exclusion have been replaced by the phenotype approach.
Risk factors of AD and cognitive impairment include cerebrovascular disease (CVD, Stroke), silent infarcts and white matter lesions as a surrogate of small vessel disease (WMLs). Increased AD risk relates to arterial hypertension, high cholesterol, obesity, diabetes, atherosclerosis, major depression and head trauma. Lower AD risk factors include high education, physical activity, social activity, antioxidants, fish oil, treatment of arterial hypertension and use of statins. Probability of late-life AD can be related to a midlife Risk Score.
Vascular Cognitive Impairment (VCI) concept covers spectrum of vascular aetiologies including AD+CVD and a spectrum of severity from impairment in one or two cognitive domains to a more global syndrome. VCI is shifting old "dementia thinking" from thresholds (as the old Alzheimerized dementia) to a continuum of cognitive impairment, from the late to early stages and from effects to causes.
VCI relate to complex interactions between vascular aetiologies (different types of CVD, vascular risk factors), changes in the brain (infarcts, ischemic WMLs, atrophy, but also AD type changes) and host factors (age, education, genetics). One category is post-stroke cognitive impairment and dementia; cognitive impairment post-stroke is seen in 60% and dementia in 25% of patients with ischemic stroke aged 55 to 85 years. The two major forms of VCI relate to "the stroke brain" i.e. large vessel disease and cardiac embolic events, and "the network brain" i.e. small vessel disease.
Brain as end-organ approach focuses especially on the executive small vessel anterior network- brain, which is known to be the largest endothelial organ of the human economy. Subcortical vascular disease and dementia (SIVD) is the main subtype of VCI, the small vessel prototype.
Confluent WMLs seen on magnetic resonance imaging are surrogate of small vessel disease. The European LADIS-study showed how confluent WMLs relate even in short term to bad clinical outcomes: disability, death, cognitive decline, depression, impaired ADLs, impaired gait and stability, urinary problems and stroke.
AD+CVD. In unselected neuropathology series prevalence of AD+CVD is high (50 to 70%). Already Alzheimer (1906) and Tomlinsson et al. (1070) recognized AD+CVD, which long has been underestimated CVD, especially small vessel disease, relate to an earlier expression of clinical AD syndrome, as do the independent vascular risk factors.
The secret partners AD and CVD (Stroke) are challenging our brain health. In persons aged 65 years of age, every 1 of 3 men and 1 of 2 female have a lifetime risk to have AD, CVD or AD+CVD; which is the main challenge of independent life style in the coming years.
Where to invest. The general stock market has disappointed many of us. However, to invest on brain health; treatment of risk factors (CVD primary and secondary prevention) and promotion of protective factors is know to give secure growth to our investments in long run. Why not start today.

IMPROVED PROGNOSIS OF COGNITIVE CHANGE IN HEALTHY AGED AND MCI SUBJECTS: IS THERE STILL A NEED FOR PLACEBO CONTROL IN PREVENTATIVE CLINICAL DRUG TRIALS?

René Spiegel[1], Manfred Berres[2], André Misérez[1], Andreas U. Monsch[1]
[1]Memory Clinic, Geriatric University Hospital Basel, Switzerland;
[2]RheinAhrCampus Remagen, University of Applied Sciences Koblenz, Germany

Prospective, randomized, placebo-controlled, double-blind clinical trials (RCCTs) are today's Gold Standard of therapeutic research studies in neuro-psychopharmacology. It is assumed that RCCTs protect the results of such studies against the two most important confounding factors: the effect of time (presenting, e.g., as spontaneous changes in the course and presentation of a disorder) and the impact of attitudes and expectations affecting all participants of a trial. On the other hand, the use of placebo is ethically problematic in therapeutic studies of diseases that can cause serious or irreversible harm to the subjects. This clearly applies to trials that involve subjects with Mild Cognitive Impairment (MCI) or patients in early stages of Alzheimer Disease (AD), since both conditions are more or less likely to have a fatal outcome. Despite the ethical dilemma, regulatory authorities as well as internationally renowned experts still recommend the use of placebo in trials with MCI and early AD patients, studies that may last several years. In this talk we will discuss the potential benefits and pitfalls of omitting the use of placebo in long-term preventative studies of MCI and AD. It is proposed to replace placebo control by making full use of the knowledge and available data about the risk factors, pathophysiology and time course of MCI and AD.

FRIDAY, JUNE 12, 2009

III EVIDENCE BASED DIAGNOSTIC TOOLS

Chairpersons: Kaj Blennow and Hilkka Soininen

12:30-13:00	**MRI as a tool for the differential diagnosis of dementia** Niels Prins, Vrije University, Amsterdam, The Netherlands
13:00-13:30	**Role of CSF markers in the diagnosis of AD** Kaj Blennow, University of Göteborg, Sweden
13:30-14:00	**Diagnostic value of SPECT and PET** Juha Rinne, University of Turku, Finland
14.00–14.30	Coffee break

IV NEW CLINICAL CRITERIA FOR ALZHEIMER'S DISEASE

Chairpersons: Timo Erkinjuntti and Niels Prins

14:30-15:00	**Early cognitive changes in Alzheimer's disease** Pieter Jelle Visser, University of Maastricht, The Netherlands
15:00-15:30	**Identification of prodromal AD with serial neuropsychological tests** Jean-Marc Orgogozo, University of Bordeaux, France
15:30-16:00	**New concept and new diagnostic criteria for Alzheimer's disease** Bruno Dubois, Salpêtrière Hospital, France
16:00-16:30	**General discussion**
19.00-23.00	**Get-together Party and Posters** Scandic Hotel Kuopio

MRI AS A TOOL FOR THE DIFFERENTIAL DIAGNOSIS OF DEMENTIA

N.D. Prins and Ph. Scheltens
Dept of Neurology and Alzheimer Center, VU University Medical Center, Amsterdam, The Netherlands

Neuroimaging is no longer optional in diagnosing the underlying disease in dementia. Structural and functional imaging techniques have evolved over time in terms of resolution, availability and costs. MRI without contrast is the preferred imaging modality for the differential diagnosis of dementia and the protocol should include at least coronal high resolution T1-weighted images for the assessment of medial temporal lobe atrophy (MTA) and axial T1-weighted images for the assessment of global brain atrophy. Axial T2-weighted images, FLAIR and proton density-weighted images are crucial for the detection of cerebrovascular pathology, including lacunes and cerebral white matter lesions. Axial gradient-echo T2*-weighted images are needed to detect microbleeds and calcifications. At present SPECT and PET are second-line investigations employed when MRI is inconclusive (e.g., in early AD and FTD cases). Imaging should always be used in conjunction with the clinical findings and never on its own. Some images are, however, diagnostically so evident that they often 'make the case' for instance in Semantic dementia (SD) and Corticobasal degeneration (CBD). By far, the evidence for hippocampal atrophy in AD exceeds that of the other imaging modalities. Specificity of hippocampal atrophy towards other dementias and age however is an issue that needs to be resolved. Using MRI to differentiate AD from other disorders is now common practice and is proposed also to be used in the new criteria that enable a diagnosis of AD before dementia occurs.

ROLE OF CSF MARKERS IN THE DIAGNOSIS OF AD

Kaj Blennow
Dept. of Clinical Neuroscience, University of Göteborg, Sahlgren's University Hospital, Mölndal, Sweden

Research advances during the 25 years have given detailed knowledge on Alzheimer's disease (AD) pathogenesis. Detailed information is now by hand on the molecular mechanisms of APP processing and β-amyloid (Aβ) production, and the aggregation of Aβ with plaques development, a process believed to result in loss of synaptic integrity and progressive neurodegeneration. These research advances have also been translated into several new drug candidates with disease-modifying potential, several of which are now evaluated in clinical trials. This new type of drugs will logically most effective in the earlier stages of the disease, before the neurodegenerative process is too severe. Thus, the promise of causal treatment beyond symptomatic therapy also generates a need for diagnostic methods, to enable early diagnosis of AD.
The cerebrospinal fluid (CSF) is in direct contact with the extracellular space of the brain, and thus biochemical changes in the brain are reflected in the CSF. The CSF biomarkers total tau (reflecting neuronal degeneration), Aβ42 (reflecting plaque formation), and phosphorylated tau (reflecting tau phosphorylation state and tangle formation), have in numerous studies been found to have a high diagnostic value for AD, to differentiate AD from normal aging and several important differential diagnoses. Large follow-up studies also show that these CSF biomarkers with high accuracy can identify which patients with mild cognitive impairment (MCI) that will progress to AD (i.e., have incipient AD), and differentiate from benign MCI cases.
CSF biomarkers may also be valuable tools to identify and monitor the biochemical effect of new Aβ modulatory drug candidates directly in living AD patients. By CSF analyses, many aspects of the APP/Aβ metabolism can be monitored, including all Aβ isoforms (Aβ42, Aβ40 and others), APP isoforms (α-sAPP and β-sAPP), and secretase (BACE1) activity. Recent studies also show that the intra-individual variation in these CSF biomarkers is remarkably low both during 6 and 24 months. This suggests that CSF biomarkers have the potential to identify very minor biochemical changes induced by Aβ modulatory treatment.

DIAGNOSTIC VALUE OF SPECT AND PET

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

With positron emission tomography (PET) and single photon emission computed tomography (SPECT) it is possible to study blood flow, oxygen consumption, glucose metabolism or the functioning of various neurotransmitter systems in living human brain.
Cerebral blood flow and glucose metabolism studies show typical findings in different dementing diseases. In Alzheimer´s disease (AD) there is usually bilateral, temporo-parietal hypometabolism. On the other hand, in frontotemporal dementia (FTD) the hypometabolism is concentrated in frontal and anterior temporal lobes. This pattern of hypometabolism can be used in the differential diagnostics between AD and FTD. In vascular dementia there is no specific pattern of hypometabolism, but the reduction is patchy depending on the location of ischemic changes. In dementia with Lewy bodies (DLB) there is also hypometabolism in the visual cortices, whereas these areas are relatively well preserved in AD. This might serve as a differential diagnostic aid to distinguish DLB from AD, but further studies are needed to confirm this.

Studying neurotransmitter systems could increase specificity in the sense that in various dementing disease different neurotransmitter systems are preferentially impaired. For instance in AD impairment of the brain cholinergic system is the most severe and consistent biochemical deficit, whereas in Parkinson´s disease (PD) dysfunction of brain dopaminergic system is the biochemical hallmark. This far studying striatal dopaminergic function to differentiate DLB from AD seems to be most promising clinical application of SPECT or PET.
More recently ligands have been developed that bind to typical protein aggregations seen in different dementing diseases. In AD there is accumulation of beta-amyloid which deposits as plaques. Nowadays there are several PET and SPECT ligands that bind to these protein aggregations. Amyloid imaging has several potential applications such as early diagnosis and differential diagnosis, follow-up, detection of asymptomatic cases, development of treatment and monitoring of treatment effects. Patients with AD show clear increase of uptake in the cortical areas and this is also seen in many patients with mild cognitive impairment, most of whom have converted to AD during follow-up. The uptake is generally normal in patients with PD and FTD whereas a considerable proportion of patients with DLB show increased uptake suggesting the existence of concomitant AD-pathology. Follow up studies in healthy controls showing increased amyloid accumulation on one hand and in AD patients being negative in amyloid imaging would reveal interesting information about the role and time course of amyloid accumulation in AD and the usefulness of amyloid imaging in the early diagnosis and differential diagnosis of AD.

EARLY COGNITIVE CHANGES IN ALZHEIMER'S DISEASE

Pieter Jelle Visser
Department of Psychiatry, University of Maastricht, Maastricht; Department of Neurology, VU University Medical Centre, Amsterdam, The Netherlands

Background: Cognitive impairments are among the earliest symptoms of Alzheimer's disease (AD). Aim of the study is to investigate how these symptoms can be used for the diagnosis of AD in non-demented subjects.
Methods: Non-demented subjects with cognitive impairments were selected from the DESCRIPA study, a prospective cohort study of 881 subjects recruited from 20 memory clinics across Europe (www.descripa.eu). Predictors for AD tested included a variety of clinical, cognitive, imaging, and CSF markers. Outcome measures were AD-type dementia or memory impairment (either AD-type dementia or amnestic MCI) at a 2 or 3-year follow-up. We also investigated the predictive value of the new AD research criteria. Predictive accuracy was expressed as an Area under the Curve (AUC) of a Receiver Operating Characteristic curve.
Results: In univariate analysis memory impairment was the best predictor for AD or memory impairment (AUC=0.80-0.83). The best combination of predictors for AD was age, memory impairment, fluency, MMSE score, and body mass index (AUC=0.85). The best combination of predictors for memory impairment was age, memory impairment and the ratio of beta amyloid 1-42 and total tau in CSF (AUC=0.93). The predictive accuracy for AD or memory impairment according to the research criteria was 0.69.
Conclusions: Memory impairment is a strong predictor for AD, but the best predictive accuracy can be obtained if memory impairment is combined with other markers of AD.

IDENTIFICATION OF PRODROMAL AD WITH SERIAL NEUROPSYCHOLOGICAL TESTS

J-M Orgogozo*, H Amieva, M Le Goff and J-F Dartigues*
Inserm Unit 897 and Division of Clinical Neurosciences, University of Bordeaux, France*

Background: Cognitive deficits are detectable long before AD dementia but it is still uncertain when neuropsychological tests begin to decline. As the prodromal AD phase is of long duration it would be of value to reliably select patients at this stage, first for clinical trials then for early treatment. Neither CSF biomarkers nor brain imaging are validated at this asymptomatic stage.
Methods: In the PAQUID study, the neuropsychological decline over a 14-year period before AD dementia with the MMSE, the IST, the BVRT and the WST showed a distinct temporal pattern. We identified, by principal component analyses (PCA), a subtest of episodic memory derived from the MMSE. A short questionnaire on 4 IADLs was used to assess function. Memory complaints were asked for by simple questions and depressive symptomatology by the CES-D. The evolution of scores over time was described using a semi-parametric extension of the mixed effects linear model. As individual scores are very sensitive to educational level we searched for change points in the curves of each measure, as early markers of abnormal decline.
Results: Of the 3,777 baseline subjects, 350 subjects developed AD during follow-up, matched to 350 controls.
In future AD the first declines appeared 11-13 years before dementia at the IST and the WST. The MMSE and the BVRT separated later, around 8 years pre-dementia. The episodic memory subscale identified by PCA, with the 5 items "orientation to time" and the 3 items "delayed words recall" began to fall 5-7 years before dementia and was a better predictor of incident AD than the complete MMSE. The IADL subscale scores separated sharply at minus 5 years. Finally the apparent change points in the curves were at 10-11 years for the IST, 9-10 years for the WST the BVRT, 8-9 years for the MMSE and 6-7 for episodic memory. In all tests a second, sharper, change point occurred at 3-4 years. The IADL change point occurred at minus 4 years.
Conclusions: the simple tests presented have the potential to screen prodromal AD long before the present biomarkers and diagnostic tests become sensitive and reliable. These results show that the window of therapeutic opportunity before dementia in AD may last for as long as ten years.

NEW CONCEPT AND NEW DIAGNOSTIC CRITERIA FOR ALZHEIMER'S DISEASE

Bruno Dubois
INSERM-UPMC UMRS 610, Federation of Neurology, Salpetriere Hospital; University of Paris6, Paris, France

The criteria of the NINCDS-ADRDA for AD represent the prevailing diagnostic standards in research. While these sets of criteria represented an important step forward following their publication, they have now fallen behind the unprecedented growth of scientific knowledge of the disease from its earliest clinical manifestations through postmortem histopathology. Distinctive and reliable biomarkers of AD are now available through structural brain imaging with Magnetic Resonance Imaging (MRI), molecular neuroimaging with Positron Emission Tomography (PET) and cerebrospinal fluid (CSF) analyses. This progress provides the impetus for the revised research diagnostic criteria for AD. Our proposed diagnostic framework was developed through an international working group 2005, who determined by consensus that a set of revised AD criteria could be developed to capture both the earliest stages, prior to full-blown dementia, as well as the full spectrum of the illness. These new criteria are centered on a clinical core of early and significant episodic memory impairment. They stipulate that in addition there must also be at least one or more abnormal biomarkers amongst structural neuroimaging with MRI, molecular neuroimaging with PET and CSF analysis of amyloid β/tau proteins. The timeliness of these criteria is underscored by the myriad of drugs currently under development that are directed at altering the disease pathogenesis. Validation studies within both existing and prospective cohort studies will be needed to advance these criteria and optimize their sensitivity, specificity and accuracy. The strength of these proposed research criteria is the introduction of neurobiological measures onto the clinically based criteria.

SATURDAY, JUNE 13, 2009

THERAPEUTIC OPTIONS IN MEMORY DISEASES

V SYMPTOMATIC TREATMENT - Assessment of efficacy
Chairpersons: Ezio Giacobini and Bengt Winblad

08:00-08:30	**Omega-3 fatty acids in the prevention and treatment of AD** Yvonne Freund-Levi, Department of Geriatrics, Karolinska University Hospital, Sweden
08:30-09:00	**Present and emerging treatments for Alzheimer's disease** Bengt Winblad, Karolinska Institutet, Sweden
09:00-09:30	Coffee break
09:30-10:00	**Role of cholinesterase inhibitors in Lewy body dementias** Murat Emre, Department of Neurology, Istanbul University, Turkey
10:00-10:30	**Alternative ways of cholinergic modulation** Abraham Fisher, Israel Institute for Biological Research, Israel
10:30-11:00	**Treatment of Alzheimer‘s disease: Why so many drugs have failed?** Ezio Giacobini, University of Geneva Medical School, Switzerland
11:00-11:15	***Awards Ceremony***

VI LIPIDS AND ALZHEIMER'S DISEASE
Kuopio University Neuroscience Centre Symposium
Chairpersons: Heikki Tanila and Tobias Hartmann

11:15-11:45	**APP processing and amyloid ß-peptides, a molecular sensor for cellular lipid levels** Tobias Hartmann, University of the Saarland, Germany
11:45-12:15	**Impact of dietary lipids on cerebral blood flow and amyloid pathology in animal models** Amanda Kiliaan, Radboud University Nijmegen, The Netherlands
12:15-13:15	Lunch break
13:15-13:45	**Adiposity, hyperinsulinemia, diabetes, and Alzheimer's disease** Jose Luchsinger, Columbia University, USA
13:45-14:15	**Role of statins in prevention and treatment of AD** Benjamin Wolozin, Boston University, USA
14:15–14:45	Coffee break

OMEGA-3 FATTY ACIDS IN THE PREVENTION AND TREATMENT OF AD

Yvonne Freund-Levi
Department of Geriatrics, Karolinska University Hospital, Stockholm, Sweden

Background: ω-3 fatty acids (ω-3 FA) found in dietary fish or fish oils are anti-inflammatory agents that may influence Alzheimer's disease (AD).
Objective: To study effects of dietary ω-3 FA supplementation on inflammatory markers in cerebrospinal fluid (CSF) and plasma from patients with mild to moderate AD.
Methods*:* Thirty-five patients (70.3 years ± 8.2) were randomized to a daily intake of 2.3 g ω-3 FA or placebo for 6 months. The inflammatory markers IL-6, TNF-α and sIL-1RII were analyzed in CSF and plasma at baseline and at 6 months. The AD markers tau-protein (T-tau), hyperphosphorylated tau-protein (P-tau) and β-amyloid ($A\beta_{1-42}$) were assessed in CSF. High sensitivity C-reactive protein, (hs-CRP) was assessed in plasma. A possible relation to the *APOE* genotype was investigated
***Results*:** There was no significant treatment effect of ω-3 FA on inflammatory and AD biomarkers in CSF or on inflammatory markers in plasma, nor any relation with *APOE*. A significant correlation was observed at baseline between sIL-1RII and $A\beta_{1-42}$ levels in CSF.
***Conclusions*:** Treatment of AD patients with ω-3 FA for 6 months did not influence inflammatory or biomarkers in CSF or plasma. The correlation between sIL-1RII and $A\beta_{1-42}$ may reflect the reciprocal interactions between IL-1 and Aβ peptides.

PRESENT AND EMERGING TREATMENTS FOR ALZHEIMER'S DISEASE

Bengt Winblad
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Elderly patients constitute an escalating proportion of the population resulting in an increased prevalence of Alzheimer Disease (AD). Treatment regimens throughout the different stages of dementia vary, with objectives broadening as the disease progresses and patients experience a deterioration of their symptoms. In the early stages of AD, an active patient role is encouraged and residual abilities are important. In severe dementia, in addition to treating the patient, means of reducing the burden on both the caregiver and health system must be considered. The pharmacoeconomic aspects of dementia are important. The cost of treating AD is high and the financial burden increases as the disease progresses.
Acetylcholinesterase inhibitors have been approved for treatment of mild to moderate AD. Two studies have been positive in moderately severe and severe AD. The NMDA-antagonist memantine has shown to be effective in moderate to severe AD. A pharmacoeconomic study showed that treatment with memantine reduced caregiver time and delayed institutionalisation, ie was cost effective. Furthermore a study in moderately severe and severe AD with the combination donepezil and memantine was very positive. Memantine is in Europe and US approved for moderate to severe AD, and donepezil is in US approved also for severe AD.
Rivastigmine patches were shown to be as effective as capsules but with only one-third of gastrointestinal side effects and are now approved worldwide. Patches were also shown to be preferred by the caregivers.
A new approach targeting the mitochondrial function has been tested in a Russian study with an antihistaminic drug (Dimebon) with very positive outcome. A confirmatory study is currently being performed in a number of European countries, Russia, Chile and US. Basic research studies to reveal the underlying mechanisms of action are ongoing.
Recent years, focus has more and more been put on early diagnosis and treatment. New biomarkers have been developed and are under validation. Biomarkers in CSF, eg Aß40, Aß42, tau and p-tau, have been established to support the clinical diagnosis and also as a marker to follow treatment effects for disease-modifying drugs. Several ligands are being developed for PET imaging of Aß, so far PET-PIB is the most established. These new biomarkers are used eg to evaluate the effect of passive and active "vaccination" studies currently being performed.

ROLE OF CHOLINESTERASE INHIBITORS IN LEWY BODY DEMENTIAS

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Dementia associated with Parkinson's disease (PDD) and Dementia with Lewy Bodies (DLB) share many clinical, pathological and biochemical features. The most consistent biochemical deficit found to be associated with both disorders is cholinergic. After the cholinesterase inhibitors (ChE-I) became available for the treatment of Alzheimer's disease all commercialy available ChE-I have also been tried in both disorders. Most of the published studies involve small groups, the majority are open label studies or case series. One large, randomized, placebo controlled study each was conducted with rivastigmine in both conditions, and one large randomized controlled study was performed in PDD with donepezil. The study in DLB revealed that rivastigmine provided benefits in behavioral symptoms and cognitive functions such as improvement in attention. Likewise the large study with rivastigmine in patients with PDD demonstrated that there were significant differences to placebo in all symptom domains including cognitive functions, behavioral symptoms and overall functioning. Beneficial effects on cognitive functions and global change scores were also seen with donepezil in PDD patients. In general the adverse events were mainly gastrointestinal, there was no significant worsening in motor symptoms in the objective scales, in the PDD study a worsening of tremor was reported as an adverse event in 10% of the patients. Based on the results of the EXPRESS study rivastigmine was approved as the first specific treatment for patients with mild to moderate PDD.

ALTERNATIVE WAYS OF CHOLINERGIC MODULATION

Abraham Fisher[1], Antonella Caccamo[2], Salvatore Oddo[2], Rachel Brandeis[1], Hanoch Elkon[1], Niva Natan[1], Nira Barner[1], Zippora Pittel[1], Frederic Checler[3], and Frank M. LaFerla[2]

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Select ways of cholinergic modulation for the treatment of Alzheimer's disease (AD) can include: cholinesterase inhibitors, M1 muscarinic receptor (M1 mAChR) orthosteric and allosteric agonists, alpha4beta2- or alpha7-nicotinic agonists. The pros and cons of such cholinergic modulations are reviewed with emphasis on M1 selective muscarinic agonists (e.g. AF102B, AF150(S), AF267B and AF292) and the M1 mAChR's pivotal role in several CNS diseases (*e.g.* AD, DLB, CAA, schizophrenia, prion diseases). Such orthosteric M1 agonists *via* M1AChR-modulation of PKC-ADAM17 and PKC-GSK3beta pathways, respectively – i) elevated alpha-APPs, the non-toxic N1 fragment of PrP^c and decreased beta-amyloid levels; and ii) decreased beta-amyloid-induced neurotoxicity and tau hyperphosphorylation. These agonists have a wide safety margin and restored cognitive deficits, cholinergic markers, and decreased CSF beta-amyloid42 in rabbits and tau-proteins hyperphosphorylation in several animal models. AF267B removed vascular beta-amyloid42 deposition from cortex in cholinotoxin-treated rabbits. In 3xTgAD mice AF267B rescued cognitive deficits and decreased beta-amyloid42 and tau pathologies in the cortex and hippocampus, *via* M1AChR-activation of ADAM17 and M1AChR-decrease of BACE1 and GSK3beta steady state levels. Compared with other cholinergic treatments, direct activators of alpha-secretase, or inhibitors of BACE1, gamma-secretase and GSK3beta, respectively, selective M1 agonists, by mimicking acetylcholine-mediated normal M1AChR-physiology on these enzymes, would appear safer. Due to an elusive etiology of AD, a disease-modifying treatment should target major AD hallmarks, yet without enhancing anyone of them, and AF267B is the 1st reported monotherapy that meets this challenge. Clinical trials will determine if M1 agonists may become an important therapy in AD and/or other CNS diseases.

TREATMENT OF ALZHEIMER'S DISEASE: WHY SO MANY DRUGS HAVE FAILED?

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The year 2008 marked the set back of three major clinical trials directed to prevent aggregation or accumulation of beta-amyloid by means anti-aggregants, gamma-secretase modulation or passive immunization. Preventive therapy has been equally negative. Why do so many drugs for AD have failed in development? Do we need to rethink the amyloid hypothesis, change the approach and the target, or rethink the trials? We propose that the realities of AD, especially the progression of neuropathology prior to the onset of clinical symptoms require to privilege biomarkers and signs capable of differentiating individual at risk as surrogate targets for preventive treatment, testing and use in clinical trials.(2)

References

1. Ezio Giacobini and Robert E. Becker. One hundred years after the discovery of Alzheimer's Disease.A turning point for therapy?Journal of Alzheimer Disease 12 (2007) 37-52
2. Robert E.Becker, Nigel H.Greig and Ezio Giacobini
Why so many drugs for Alzheimer'Disease fail in development? Time for new methods and new practices?Journal of Alzheimer's Disease 15 (2008) 303-325

APP PROCESSING AND AMYLOID ß-PEPTIDES, A MOLECULAR SENSOR FOR CELLULAR LIPID LEVELS

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Cholesterol has received special attention in AD, because it influences Aß (amyloid – beta) production, epidemiological studies show a clear correlation between high cholesterol and increased AD risk and because some cholesterol lowering drugs correlate with a reduced risk for dementia.
Aß is a proteolytic processing product generated from the amyloid precursor protein APP. APP processing is part of a sensor system that responds to alterations in the lipid composition of cellular membranes. This system is highly sensitive to alterations in certain lipids, whereas it is entirely insensitive to others. E.g. cholesterol strongly activates amyloidogenic APP processing, resulting in increased Aß release. Phosphatidylethanolamins however, typically don't affect APP processing.
The increased Aß production and other APP processing events caused by cholesterol, trigger several regulatory feedback actions, including the activation and inhibition of key lipid metabolism enzymes, that together aim to reset the brains lipid homeostasis. Although cholesterol is the best-studied brain lipid in AD, many other lipids are involved in the Aß-lipid regulatory system and some of these other lipids exceed the cholesterol effect on Aß production greatly. To identify these lipids allows not only to understand the Alzheimer's disease better, but also to identify potential interventions like statins or the omega-3 fatty acid DHA. Thus far we were able to identify 5 lipid classes, involved in Aß regulation.
One factor that recently gathered more attention are fatty acids. Most fatty acids have no or only marginal effects on amyloid metabolism, but some significantly increase or decrease Aß generation. Especially interesting are the Aß reducing abilities of some omega-3 polyunsaturated fatty acids, especially the DHA mentioned above and the EPA.
These findings add to a rising number of results that help to understand the significant impact the lipid metabolism has in Alzheimer's disease. The future challenge will be to decipher the molecular pathways which link neurodegeneration and lipids in Alzheimer's disease and to use develop save and effective prevention and early therapy of Alzheimer's disease.

IMPACT OF DIETARY LIPIDS ON CEREBRAL BLOOD FLOW AND AMYLOID PATHOLOGY IN ANIMAL MODELS

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Background. High serum cholesterol and low docosahexanoic acid (DHA) intake are risk factors for Alzheimer's disease (AD). However, how these parameters influence AD pathology is still a topic of debate. We investigated the influence of cholesterol and DHA containing diets on cognition, amyloid beta (Aβ) deposition, cerebral energy metabolism and relative cerebral blood volume (rCBV) in the APP/PS1 mouse model of Alzheimer's disease. **Methods**. 2 months old APP/PS1 mice and their control wild type littermates were fed regular rodent chow, or a diet with DHA or cholesterol for 6, 13 or 16 months. rCBV in brain areas was determined with T2 weighted gradient echo MRI, using ultra small paramagnetic particles of iron oxide (USPIO) as contrast agent. Aβ deposition was quantified in hippocampal (CA1, CA3, DG) and cortical regions by immunohistochemistry. Spatial Memory and learning were measured with the Morris Water Maze test and cerebral energy status and metabolism was quantified with MRS, **Results**. We showed that DHA improved spatial memory, decreased Aβ deposition and increased rCBV in APP/PS1 mice, indicating that a DHA-enriched diet can diminish AD-like pathology. In contrast, TWD diets decreased rCBV and APP/PS1 mice on a TWD diet showed an increase in plaque load. **Conclusions.** The present data indicate that long-term dietary interventions change AD-like pathology in APP/PS1 mice. Additionally, effects of the tested diets on vascular parameters were observed before effects on Aβ load were noted. These data underline the importance of vascular factors in the APP/PS1 mouse model of AD pathology

ADIPOSITY, HYPERINSULINEMIA, DIABETES, AND ALZHEIMER'S DISEASE

José A. Luchsinger
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Background: This presentation will provide a review of the epidemiologic evidence linking the continuum of adiposity, hyperinsulinemia, and type 2 diabetes (T2D) with Alzheimer's disease (AD). **Methods:** Most of the data shown is from a longitudinal study of aging in Northern New York City. **Results:** The mechanisms linking this continuum to AD may include hyperinsulinemia, advanced products of glycosilation, cerebrovascular disease, and products of adipose tissue. Elevated adiposity in middle age is related to a higher AD risk, but the data in old age is conflicting. This association is attenuated in older ages, and measures of central adiposity may capture this relationship better than measures such as body mass index. Hyperinsulinemia, a consequence of higher adiposity and insulin resistance is also related to higher AD risk. Hyperinsulinemia precedes T2D, and T2D is also related with higher AD risk. The association between this continuum and AD has strong biologic plausibility. This continuum is a cause of cerebrovascular disease, which has an important role in AD. In addition, hyperinsulinemia may be important in the clearance of amyloid beta, the culprit of AD. **Conclusions**: a large proportion of the world population may be at increased AD risk given the trends for increasing prevalence of elevated adiposity, hyperinsulinemia, and T2D. However these associations may present a unique opportunity for AD prevention and treatment. Several studies in the prevention and treatment of T2D are currently conducting cognition ancillary studies. Clinical trials using insulin sensitizers in the treatment or prevention of AD are under way.

ROLE OF STATINS IN PREVENTION AND TREATMENT OF AD

Benjamin Wolozin, Nien-Chen Li, Austin Lee and Lewis Kazis
Boston University School of Medicine and School of Public Health, Boston, USA

Background: Epidemiological studies suggest that mid-life hypercholesterolemia is a risk factor for dementia, and that statins are associated with a lower incidence of AD prompted a great hope and a flurry of research. The link between cholesterol use and the pathophysiology of AD has been confirmed in cell culture and in animal models. However, clinical translation has been disappointing. **Methods**: Rates of AD and dementia among users of statins, angiotensin receptor blockers, and other cardiovascular medications will be presented using a prospective cohort analysis. Biochemical studies of the actions of statins in the brain will also be presented. **Results**: We observe that statins are associated with changes in APP processing in cell culture, as well as changes in inflammatory markers and small GTPases in the brain. A detailed analysis of epidemiological studies raise significant questions about the data on statins obtained from retrospective cohorts. For instance, we did not observe a dose-response relationship between statin use and incidence of AD. In contrast, our cohort analyses of angiotensin receptor blockers show a robust pharmacological profile. **Conclusions**: The putative cognitive benefits of statins might not be too weak to help patients with existing AD. In contrast, our results show hope for a new class of medications that might be useful for subjects with or at risk for AD.

SATURDAY, JUNE 13, 2009

THERAPEUTIC OPTIONS IN MEMORY DISEASES

VII REHABILITATION IN DEMENTIA

Chairpersons: Daniel Michaelson and Kaisu Pitkälä

14:45-15:15 **Synergistic pathological interactions between apolipoprotein ε4 amyloid–β and environmental stimulation**
Daniel Michaelson, Tel-Aviv University, Israel

15:15-15:45 **Multidisciplinary interventions in dementia care**
Kaisu Pitkälä, University of Helsinki, Finland

15:45-16:15 **A randomised controlled trial investigating the clinical and cost effectiveness of an evidence-based cognitive stimulation therapy (cst) programme for people with dementia**
Martin Orrell, University College London, UK

16:15-16:30 **Closing remarks**
Hilkka Soininen, Chairperson of the Organizing Committee
University of Kuopio, Finland

SYNERGISTIC PATHOLOGICAL INTERACTIONS BETWEEN APOLIPOPROTEIN E4 AMYLOID–β AND ENVIRONMENTAL STIMULATION

Daniel M. Michaelson
Department of Neurobiology , Tel Aviv University, Israel

Background: Activation of the amyloid cascade by inhibition of the Aβ-degrading enzyme neprilysin results in isoform specific degeneration of distinct groups of neurons in apoE4 mice which is accompanied by the accumulation of intracellular Aβ and apoE and by cognitive deficits. We presently investigated the cellular mechanisms underlying this apoE4-Aβ cross talk and its possible role in mediating the pathological phenotypes of apoE4. **Results:** Confocal microscopy revealed that the degeneration of CA1 hippocampal neurons in apoE4 mice following activation of the amyloid cascade, but not that of the corresponding septal neurons, is associated with lysosomal activation and the oligomerization of the accumulated Aβ and with inflammatory activation. Neuronal plasticity experiments revealed that apoE4 inhibits synaptogenesis and neurogenesis and stimulates apoptosis in hippocampal neurons of apoE4 mice that have been exposed to an enriched environment, and that these effects are associated with the specific accumulation of intracellular Aβ in the affected apoE4 neurons. Further experiments revealed that apoE4 up-regulates the expression of inflammation-related genes following treatment with LPS, and that this effect is also associated with the accumulation of intraneuronal Aβ in hippocampal neurons. **Conclusions:** These findings suggest that the synergistic pathological interactions between apoE4 and Aβ following activation of the amyloid cascade are mediated via distinct neuron specific mechanisms which may play a role in the impairments in neuronal plasticity and brain inflammation triggered by apoE4.

MULTIDISCIPLINARY INTERVENTIONS IN DEMENTIA CARE

Kaisu Pitkälä
University of Helsinki, Finland

Dementia affects comprehensively both patient and her/his family. Consequences of dementia include effects on global cognition, behaviour, physical, psychological and social functioining, need for health and social services, as well as economy and quality-of life of both patient and her/his family. In addition, patients often suffers from multiple diseases and disabilities related to them. Therefore, effective intervention often requires multidiciplinary approach and professional expertice both in dementia care and in geriatric assessment.
Multidiciplinary interventions in dementia care may be examined from several point of views. Besides comprehensiveness of the intervention (e.g targetting on global cognition, behavioral symptoms, disabilities or all), it may be considered whehter the intervention handles patient or his/her partner/family or both. The content of the intervention is utmost important: who does what and how; what kind of expertice and know-how do the key intervening persons/teams have, what kind of resources do they have? It is essential to know, to what kind of patient group is the intervention targeted on: age group; patients living alone or with their partner; MCI, mild, moderate or severe dementia; what kind of comorbidities and BPSDs do the participants have? The sensitivity to change of the outcome measures is very significant when the results are interpreted.
There are tens of randomized, controlled trials examining the effectiveness of various multidiciplinary interventions in dementia care. This presentation will highlight some successful interventions and examine why they were effective. In addition, the presentation will interpret the gaps and problems related to this kind of studies.

A RANDOMISED CONTROLLED TRIAL INVESTIGATING THE CLINICAL AND COST EFFECTIVENESS OF AN EVIDENCE-BASED COGNITIVE STIMULATION THERAPY (CST) PROGRAMME FOR PEOPLE WITH DEMENTIA

Martin Orrell[1], Aimee Spector[1], Bob Woods[2] , Martin Knapp[3]
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Background: Techniques to stimulate cognition in older people with dementia are widely used around the world. Despite this there has been little systematic research into their clinical or cost effectiveness.
Methods: This single blind multicentre randomised controlled trial compared 7 weeks of a twice-weekly cognitive stimulation therapy group with treatment as usual for older people with dementia and evaluated cost effectiveness. It was carried out in 22 centres in London and South East England. Of the 201 people recruited there were 115 in the intervention group and 86 in the control group. An intention to treat analysis was carried out using analysis of covariance to control for potential variability in baseline measures. Cost data was available for 91 people who had CST and 70 who received treatment as usual. Service use was recorded prior to and during the intervention and costs calculated. A cost-effectiveness analysis was conducted with cognition as the primary outcome, and quality of life as the secondary outcome. Cost-effectiveness acceptability curves were plotted.
Results: At follow up the intervention group had significantly improved relative to the group on the ADAS-Cog ($p < 0.01$), mini-mental state examination ($p< 0.05$), and the Quality of Life-AD scale ($p < 0.05$). Using a criterion of 4 points or more improvement on the ADAS-Cog the Number Needed to Treat was 6 for the intervention group. Costs were not different between the groups. Under reasonable assumptions there is a high probability that CST is more cost-effective than treatment as usual with regard to both outcome measures. **Conclusions:** Cognitive stimulation groups may have appreciable benefits to cognition and quality of life for many people with dementia and may be more cost-effective than treatment as usual.

POSTER SUMMARY

1. VITAMIN E PLASMA LEVELS AND ALZHEIMER'S DISEASE INCIDENCE IN THE OLDEST OLD: RESULTS FROM THE KUNGSHOLMEN PROJECT

Francesca Mangialasche, Laura Fratiglioni, Patrizia Mecocci, Debora Rizzuto, Katie Palmer, Bengt Winblad, Miia Kivipelto.
Aging Research Center, Karolinska Institutet, Stockholm, Sweden; Section of Geriatrics, Perugia University, Italy.

Background: To investigate the association between plasma levels of all vitamin E isoforms (tocopherol, tocotrienols) and Alzheimer's disease (AD) incidence in very old subjects. **Methods:** The Kungsholmen Project is a population-based longitudinal study on elderly in Stockholm, Sweden. For this study, a sub-sample of 232 non-demented persons aged 80+ years was followed-up over a 6-year period to detect incident AD. Plasma levels of vitamin E were assessed at baseline with HPLC. The relation between vitamin E plasma levels and occurrence of AD was assessed with Cox regression model. **Results:** The highest tertile of total tocopherols, total tocotrienols and total vitamin E plasma levels were associated with a reduced risk of AD in comparison to the lowest tertile (total tocopherols: HR 0.55, 95% CI 0.32-0.94; total tocotrienols: HR 0.46, 95% CI 0.23-0.92; total vitamin E: HR 0.55, 95% CI 0.32-0.94). There was a significant protective effect for β-tocopherol (HR 0.62, 95% CI 0.39-0.99), and a trend for protection for α-tocopherol, α- and β-tocotrienol (α-tocopherol: HR 0.72, 95% CI 0.48-1.09; α-tocotrienol: HR 0.70, 95% CI 0.44-1.11; β-tocotrienol: HR 0.69, 95% CI 0.45-1.06). **Conclusions:** Not only α-tocopherol, but also other vitamin E isoforms may play an important role in the development of dementia in advanced age.

2. THE EFFECTS OF DIABETES MELLITUS ON NEUROPATHOLOGIC FINDINGS AT AUTOPSY

Satu Ahtiluoto[1], Tuomo Polvikoski[2], Markku Peltonen[3], Alina Solomon[1], Bengt Winblad[4], Jaakko Tuomilehto[1], Raimo Sulkava[5], Miia Kivipelto[6]
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Background: Population-based longitudinal studies have identified diabetes mellitus (DM) as a risk factor for both Alzheimer's disease (AD) and vascular dementia (VaD). The effects of DM on AD neuropathology are still unclear. **Methods:** This study is based on the Vantaa 85+ study autopsy sub-population, n=291, 22% had diabetes. Brains were fixed in phosphate-buffered 4% formaldehyde and brain autopsy performed according to the CERAD protocol for the diagnosis of AD. Logistic regression analyses were used to investigate the relationship between diabetes status and β-amyloid and tangle burden, and presence of cerebral infarcts. **Results:** Persons with diabetes were less likely to have β-amyloid deposition, 72.3% vs. 86.7%, p=0.008. In logistic regression analyses diabetes emerged as a significant protective factor against β-amyloid deposition even after adjustment for age at death, gender, education level, ApoE ε4 and dementia status (odds ratio 0.33, 95% confidence interval [CI]: 0.15-0.71). No significant differences were found between persons with and without diabetes regarding tangle burden, 56.5% vs. 67.0% respectively, p=0.135. Cerebral infarcts were significantly more common in people with diabetes, 61.3% vs. 44.4%, p=0.028. In logistic regression models controlling for age at death and gender having diabetes was a significant risk factor for cerebral infarcts (odds ratio 1.92, 95% CI 1.06-3.49). **Conclusions:** The association of diabetes with AD pathology is complex and other pathways than the amyloid cascade may be involved.

3. FINNISH GERIATRIC INTERVENTION STUDY TO PREVENT COGNITIVE IMPAIRMENT AND DISABILITY (FINGER)

Satu Ahtiluoto[1], Rainer Rauramaa[2], Hilkka Soininen[3], Tiina Laatikainen[1], Raimo Sulkava[4], Timo Strandberg[5], Jaakko Tuomilehto[6], Miia Kivipelto[1]

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Background: Time for prompt action has come following epidemiological evidence that dementia and AD share many vascular and lifestyle related risk factors with cardio/cerebrovascular diseases. The first Dementia Risk Score has been developed in the Finnish CAIDE study based on midlife risk factors.
Methods: FINGER is a multi-domain intervention study primarily designed to delay cognitive impairment among high-risk individuals. Inclusion criteria are: 1) Dementia Risk Score over 8 points, and 2) Mild memory impairment identified with CERAD test battery. Approximately 1200 subjects aged 60-74 years will be randomized to intensive intervention and regular health advice groups. The 2-year multi-domain intervention will have four main components: Nutritional guidance, Physical activity, Cognitive training and social activity, Intensive monitoring and management of metabolic and vascular risk factors. Primary outcomes are cognitive impairment measured with Neuropsychological Test Battery, and dementia. Secondary outcomes include depressive symptoms, vascular risk factors and disorders, disability, quality of life, utilization of health resources, and brain MRI measures for a sub-group. An extended follow-up is planned to evaluate dementia incidence. **Results:** The FINGER intervention is expected to result in a significant delay in cognitive decline and after an extended follow-up on dementia incidence, and have beneficial effects regarding the secondary outcomes.
Conclusions: This prospective study will provide important information of the risk factors of dementia, and novel experiences about its prevention.

4. CATEGORIZATION ABILITY IN PATIENTS WITH ALZHEIMER'S DISEASE

Kadi Epler, Margus Ennok, Ülla Linnamägi, Liina Vahter

Institute of Psychology, Department of Neurology and Neurosurgery, University of Tartu; West-Tallinn Central Hospital, Estonia.

Background: The aim of this study is to examine the categorization and abstraction skills of patients with Alzheimer's disease (AD). **Methods:** Preliminary results were obtained from a sample of 14 AD patients (mean age 67.93, mean MMSE 21.64) and 9 demographically matched control patients (mean age 67.33, mean MMSE 29.00). Subjects were tested with a categorization and memory task adapted from the Test of Categorization and Recall of Pictures (Incisia della Rocchetta, 1986). Subjects were asked to categorize a sample of 36 pictures of common items (divided into 9 subcategories) and were then asked for immediate and delayed (after 30 min) recall of the items. **Results:** AD patients grouped pictures into significantly fewer and bigger categories. They also made more placement errors (putting an item into a category where it did not belong) and overlap errors (not separating categories well enough; some items could belong to another category). Patients remembered significantly less items in immediate and delayed recall and tended to make more intrusion errors. **Conclusions:** AD affects the thinking and organization skills, patients tended to use idiosyncratic and concrete-situation associations to group pictures into categories. They relied less on semantic associations and combined the use of semantic links with experience-based associations to form categories. Their memory was also impaired.

5. PREDICTION OF TREATMENT RESPONSE TO RIVASTIGMINE IN PARKINSON'S DISEASE DEMENTIA

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Background: Rivastigmine has been found to be effective for the treatment of Parkinson's Disease Dementia (PDD). Compared to Alzheimer's Dementia (AD), PDD is characterized by a stronger cholinergic deficit. On a clinical level, cholinergic deficit may be reflected by disturbances of attention, by an impairment of short-term memory, by the presence of visual hallucinations and by increased EEG theta activity. Clinical indicators of cholinergic deficit and EEG theta activity may allow a prediction of treatment response to rivastigmine in PDD. **Methods:** In the RIVAPARK study, we examine the relationships between various indicators of cholinergic deficit and treatment response to rivastigmine in 150 outpatients with PDD. Treatment response is evaluated six and twelve months after treatment initiation. **Results:** So far, the data of 20 patients (12 men, 8 women) at ages between 64 and 83 years, with MMS scores from 15 to 27, are available. After two weeks of rivastigmine treatment, performance in an attentional task (AKT) and verbal short-term memory were significantly improved, EEG theta power had decreased. **Conclusions:** The relationship of these changes to long-term treatment response will be examined.

6. THE MEMORY AND ATTENTION TEST (MAT): AN ADAPTIVE, COMPUTER-BASED PERFORMANCE TEST FOR EARLY RECOGNITION AND TREATMENT EVALUATION IN DEMENTIA

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Background: Current memory tests are contaminated by impairments in cognitive domains other than memory and may not be individually adapted to the level of performance. We developed a computer-based adaptive Memory and Attention Test (MAT). Working memory and short-term memory are assessed in the verbal, visual and episodic domains. We evaluated the MAT considering the acceptance of this computerized test in elderly people, correlation with reference methods and recognition of patients with Alzheimer's dementia (AD). **Methods:** A preliminary analysis for the MAT subtests "Episodic working memory" (EWM) and "Episodic short-term memory" (ESTM) was carried out in a mixed group of 32 subjects, 10 men and 22 women aged between 61 and 93 years with MMS scores between 12 and 30. **Results:** Nearly all subjects could hear and see everything well, had no problem with the computer keys and felt at ease during the testing procedure. More than half of them said they would prefer the computerized testing to being tested by a person. Some stated that the computerized testing was "clear", "unequivocal" and "less embarassing". Using the subtest "logical memory" of the Wechsler Memory Scale (WMS-LM) as reference, the correlations between WMS-LM and MAT were significant, for immediate reproduction and EWM (Pearson's r=0.373; p=0.035) and for delayed reproduction and ESTM (r=0,509; p=0,003). The computerized Memory and Attention Test (MAT) was well accepted by the subjects. **Conclusions:** Correlations with the respective reference assessment were highly significant and a good separation of diagnostic groups was achieved.

7. THE CERAD-NEUROPSYCHOLOGICAL BATTERY DISCRIMINATES PATIENTS WITH MILD TO VERY MILD ALZHEIMER'S DISEASE WITH NORMAL MMSE FROM COGNITIVELY HEALTHY ELDERLY

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Background: MMSE is the commonest tool for screening dementia. MMSE score 24 or more has been used as a cut-off for excluding dementia. CERAD neuropsychological battery (nb), has been used in Finland as a screening tool for memory disorders since 1999. **Objective:** The aim of this study was to evaluate usefulness of the CERAD-nb as a screening tool for Alzheimer patients with MMSE score 24 or more. **Methods:** We compared the performance of cognitively healthy elderly (n=315) from a population based study to patients with recently diagnosed Alzheimer disease (AD) (n=171) from ALSOVA project with very mild to mild (CDR 0.5-1.0) dementia on CERAD-np. Areas under Receiver Operating Characteristic (ROC) curves (AUC) were calculated to measure the discriminatory power of the CERAD-nb tests. **Results:** 46 AD patients (26.9%) had MMSE score 24 or more, of these 30 had CDR 0.5 and 16 CDR 1.0. Patients with normal MMSE were more educated than those with MMSE score under 24 (9.2 vs. 7.1 years). Normal elderly outperformed the 46 AD patients in all CERAD-np subtests except Constructional praxis and Clock drawing. On the ROC analysis word list delayed raw score (AUC=0.924, p<.001), word list learning sum of words (AUC=0.874, p<.001), word recognition percentage (AUC=0.870, p<.001), word list delayed savings (AUC=0.824, p<.001) discriminated the groups best. **Conclusions:** The value of MMSE as a screening tool is limited at early stages of dementia, especially among patients with higher education. CERAD-nb detects cognitive changes even in very mild AD.

8. HEALTHY DIET AT MIDLIFE AND THE RISK OF LATE-LIFE DEMENTIA AND ALZHEIMER'S DISEASE

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Background:
Various nutrients and healthy diet among elderly people has been associated with a decreased risk of dementia/Alzheimer's disease (AD), but long-term effects of healthy diet on dementia remains unclear. **Methods**: Of 525 people aged 65-80 years randomly selected from population-based cohorts surveyed in 1982 or 1987, a total of 385 (73%) people were re-examined in 1998 (follow-up of 14 years) within the CAIDE study. In 1998, altogether 29 persons had dementia. Dietary habits were inquired with a survey questionnaire at midlife. For the study, a healthy diet indicator was calculated from beneficial and unhealthy components. **Results**: Persons with healthy diet at midlife had better global cognitive function in late-life (mean MMSE 26.0 vs. 25.3, p=0.043), as well as 86% decreased risk of dementia (OR 0.14, 95% CI 0.03-0.62), and 93% decreased risk of AD (OR 0.07, 95% CI 0.01-0.84) compared with persons with unhealthy diet after adjusting for demographic and vascular factors, and ApoE ε4 allelic status. **Conclusions**: Healthy diet at midlife is associated with a decreased risk of dementia/AD later in life. These findings highlight the importance of dietary patterns (instead of single nutrients) and possibly enable to more effectively prevent/delay the onset of dementia/AD.

9. β-AMYLOID PLAQUES AND TAU PROTEIN IN FRONTAL CORTICAL BIOPSY CORRELATE WITH CLINICAL ALZHEIMER'S DISEASE (AD) – KUOPIO NORMAL PRESSURE HYDROCEPHALUS REGISTRY OUTCOME STUDY

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Background: Amyloid β (Aβ) aggregates with hyperphosphorylated tau (HPτ) are diagnostic for AD. Amyloid hypothesis indicate that accumulation of Aβ in the brain initiates AD pathogenesis and could be seen years before dementia. We studied whether Aβ and/or HPτ in frontal cortical biopsies, obtained during evaluation of suspected normal pressure hydrocephalus (NPH), would predict AD diagnosis in those patients. **Methods:** From 1991 to 2006, 468 patients underwent ICP monitoring and right frontal cortical biopsy immunostained for Aβ and HPτ. By 2008, 249 patients had died in a median follow up of 4 years. All available medical records were reviewed for possible diagnosis of AD or other dementia, with adequate data on 238 of the 249 patients. **Results:** Of 238 cortical samples, 22 were Aβ+HPτ+, 85 Aβ+HPτ-, and 131 Aβ-HPτ-. Of 238 patients, 56 received clinical diagnosis of AD during follow-up. With Aβ-HPτ- as reference, the logistic regression analysis showed OD for AD 112 (95% CI 27 – 472, p<0.001) with Aβ+HPτ+ and 9.7 (95% CI 4.0 – 23, p<0.001) with Aβ+HPτ-. **Conclusions:** This is the largest follow-up study of patients assessed with right frontal cortical biopsy for suspected NPH. Aβ with HPτ, also Aβ alone, indicated later clinical diagnosis of AD rather than NPH. Brain biopsy may have a role in the verification of early AD, e.g., for preventive drug trials.

10. WHY AD PATIENTS AND CARREGIVERS PARTICIPATE IN RANDOMIZED CLINICAL TRIALS

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Background: With growing intensity of research related to Alzheimer´s disease (AD) and large numbers of patients participating in clinical trials, there is increasing interest and need to clarify patients' situation in the studies. The aim of our study was to investigate the motives and expectations of patients and their relatives for participating in the Randomized Controlled Trails. **Methods:** 19 patients with mild to moderate AD and their relatives participating in five different vaccination studies at the Memory clinic, Karolinska University Hospital, Sweden, answered a questionnaire with open and structured questions. **Results:** The result showed that the motives to participate for both patients and their relatives were to help science / contribute to research, hope for easing symptoms or cure, have access to information and possibility to have their questions answered. Patients and their relatives reported that access to medical expertise and regular health checkups were advantages of study participation. Among the disadvantages were the risk of receiving placebo, risk of side effects and harm and discomfort/pain during sample-taking and exams. Both patients and relatives reported that the desire for information was a common motive for study participating. **Conclusions:** To increase quality and compliance as well as to ensure that the ethical aspects of patient satisfaction are fulfilled in the RTC, more knowledge about patients' and their caregivers' motives and expectations of study participation is needed.

11. TISSUE MICROARRAY -TECHNIQUE IS A HIGHLY APPLICABLE TOOL IN QUALITY CONTROL OF STAININGS IN INTER-LABORATORY SETTINGS AND RESEARCH

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Background: Almost 20 years ago, Battifora described how one could create a multitissue paraffin-block that included over 100 different cores taken from several original donor-blocks. **Methods and Results:** Today, depending on the objectives, various kinds of tissue microarray (TMA) blocks including numerous cores (Ø 0.6-3-mm) can be constructed either from surgical tissue samples (e.g. cancer research) or from human postmortem material (e.g. studies of neurodegenerative diseases). In the latter case, the block can be constructed from samples from anatomical regions obtained from one subject, allowing the assessment of distribution of pathology in one-two TMA-sections. Alternatively, the block can be constructed from the same brain region obtained from the material received from different laboratories. In that case, the block can be used to study the quality differences in staining when different immunohistochemical methods are used, and furthermore, to examine the influence of pre-sectioning protocols (postmortem delay, fixation time). The TMA-technique has several advantages: TMA saves reagents, labour, and money. Furthermore, hundreds of sections can be cut for numerous analyses from one TMA-block. Importantly, all cores are treated equally throughout the staining. By using this technique, the topography-related inconsistencies in assessments can be reduced - assessors will evaluate the same anatomical region. **Conclusions:** However, this method requires both expertise and training to produce high-quality TMA-blocks.

12. OVERVIEW OF IMMUNOHISTOCHEMICAL QUALITY CONTROL STUDIES CARRIED OUT BY THE BRAINNET EUROPE CONSORTIUM

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Background. Protein aggregates containing amyloid-β, hyperphosphorylated-tau, α-synuclein, ubiquitin, p62 and TAR DNA-binding protein 43 are generally assessed in diagnostics. It is imperative for a brain-banking consortium that the neuropathologic evaluations of these proteins are comparable between the centres. During years 2004-2009, BrainNet Europe consortium has carried out several tissue microarray (TMA) technique-based inter-laboratory surveys that have allowed participants to assess their proficiencies with immunohistochemical stainings and to determine the reliability of assessment of pathological aggregates. Results of "Alzheimer's disease-related pathology" (study-I), "synucleinopathies" (II), and "amyloid-β" (III) have already been published and studies of "tauopathies" (IV) and "FTLD-U" (V) are still ongoing. **Methods.** The overall working scheme consisted of assessments of the routine techniques currently followed by participants (Trial-1), and subsequently, assessments of results when methodology was standardized (Trial-2). Furthermore, depending on the results obtained, a microscope training session was carried out before Trial-2 to reach good concordance.**Results.** TMA-method came in handy for comparison of immunohistochemical stainings. Reflecting the reality, in studies I-V, many antibodies and pre-treatments were used by participants, and consequently, staining quality and assessments differed between the participants. Harmonization of methods improved staining quality, and training was needed to yield comparative assessment results. Moreover, there were limitations in scoring/ semiquantitative assessment of immunoreactive structures. **Conclusions:** Dichotomized assessments are recommended in inter-laboratory settings.

13. HOMOCYSTEINE, HOLO-TRANSCOBALAMIN AND RISK OF ALZHEIMER'S DISEASE: A LONGITUDINAL POPULATION-BASE STUDY

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Background: Elevated total homocysteine (tHcy) levels may be caused by vitamin B12 and folate deficiency and is linked to AD in some studies. In plasma, holo-transcobalamin (holo-TC) represents the biologically active fraction of B12. This study aims to investigate the association between tHcy and holo-TC and subsequent development of AD in a prospective population-based study. **Methods:** tHcy and holo-TC were measured in plasma samples collected in 1998 from 271 non-demented participants in the population-based Cardiovascular Risk Factors, Aging and Dementia (CAIDE) study. Subjects were followed-up until 2006-2007, when presence of dementia/AD was re-evaluated. **Results:** Mean age in 1998 was 70.7 years. 17 subjects developed AD during a mean follow-up of 7.4 years. AD patients had higher tHcy (14.8 vs 12.6 μmol/l, ρ=0.01), and lower holo-TC (61.5 vs 93.3 ρmol/l, ρ=0.01) at baseline compared to non-demented persons. Increasing tHcy levels was related to an increased risk of AD; OR (95% CI) was 1.19 (1.02-1.40), even after adjusting for possible confounders. Holo-TC was associated with a decreased risk of AD; OR (95% CI) was 0.98 (0.96-0.99). Additional adjustment for folate did not change any of these results. **Conclusions:** tHcy and holo-TC are involved in the development of AD. Further evaluations are needed to assess the interplay between holo-TC and tHcy and the usefulness of holo-TC as a potential biomarker for AD.

14. PREVENTION, AN ESSENTIAL FACTOR IN THE WORK OF THE ALZHEIMER SOCIETY OF FINLAND

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Background: Increasing evidence from the scientific studies promises good primary, secondary and tertiary prevention visions for the dementing illnesses. Prevention and health promotion have been essential factors in the work of the Alzheimer Society of Finland since 2004 with the aim to prevent people from the dementing illnesses and to minimize the effects of the diseases both for the individuals and for the society. **Methods:** The Alzheimer Society of Finland has launched two primary prevention campaigns: Maintain Your Brain (2003-2005) and Life is Cool with a Fit Brain (2007-2009). In the secondary prevention area the Society is running a pilot project (2009) in cooperation with an occupational health care unit concentrating on the risk factors of dementia. In the tertiary prevention area the Society has launched two rehabilitation projects (2004-2009). **Results and Conclusions:** A memory training course model for retired people and teaching material for young people developed. The Model of Rehabilitation Services created and taken to the practise in evaluative projects in local pilot communities and local associations.The Alzheimer Society of Finland sees its role in the future very much as an intermediator between the scientific world and the everyday practice in the prevention process. It will get the parties concerned to cooperate and bring all the information available to the best possible client-centered practices.

15. MULTIVARIATE DATA ANALYSIS TO DEPICT DIFFERENCES BETWEEN ALZHEIMER'S DISEASE, MILD COGNITIVE IMPAIRMENT AND HEALTHY CONTROLS

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Background: The AddNeuroMed project is part of InnoMed (Innovative Medicines in Europe), a European Union program designed to make drug discovery more efficient. The project is designed to develop and validate novel surrogate markers in Alzheimer's disease and includes human neuroimaging. It combines MRI and MRS data with other biomarkers and clinical data. Data is collected from six different sites across Europe. **Method:** A total of 345 subjects were included in this study (117 AD, 118 MCI and 110 CTL) Data were acquired on 6 different scanners (4 GE, 1 Siemens, 1 Picker). Data acquisition was set up to be compatible with the US-based Alzheimer Disease Neuroimaging Initiative (ADNI) study. High resolution sagital 3D MP-RAGE datasets are used for image analysis. Manual hippocampus measurements were carried out using software called Hermes. Regional segmentation of the brain was carried out using the multi-scale analysis ANIMAL technique (Automated Non-linear Image Matching and Anatomical Labeling). Cortical thickness measurements were performed using the Fischl and Dale. Data were pooled together (a total of 75 variables) for a final multivariate data analysis using software SIMCA to separate the different patient groups. The method used was OPLS (orthogonal partial least square). **Results:** Using leave-one-out cross validation the OPLS model predicted 103/117 ADC and 104/110 CTL correctly, resulting in sensitivity of 88% and a specificity of 95%. Comparing ADC and MCI the model predicted 80/117 ADC and 91/118 MCI correctly (sensitivity=76% and specificity=77%). Finally when comparing MCI and CTL the model predicted 79/118 MCI and 89/110 CTL correctly (sensitivity=67% and specificity=81%). Variables of importance for the separation between the different groups were manual volume measures of hippocampus, temporal grey matter volumes and etorhinal cortical thickness measure. **Conclusion:** Multivariate data analysis is a powerful tool to distinguish between different patient groups. Combining different measures have a greater discriminant power than using them separately. Our approach may allow disease related atrophy patterns to be obtained and combinations of regional and global measures may have high diagnostic value. Revealing patterns of atrophy within the MCI group may gives us the opportunity to early distinguish which subjects will convert to Alzheimer's disease.

16. THE USE OF LEGAL GUARDIANS AND FINANCIAL POWERS OF ATTORNEY AMONG HOME-DWELLERS WITH ALZHEIMER'S DISEASE LIVING WITH THEIR SPOUSAL CAREGIVERS

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Background: We conducted a cross-sectional survey of a random sample of 1 943 spouses of home-dwellers with Alzheimer's disease (AD) to examine the prevalence of court-appointed guardians or financial powers of attorney for persons with AD, related factors and the need for information about these issues among care-giving families. **Methods:** The questionnaire consisted of variables of demographic characteristics, disability, symptoms and care needs of the person with dementia, questions about the strain of care-giving, the use of court-appointed legal guardians or powers of attorney as well as discussions about these issues – and the need for them – with a doctor. **Results:** The response rate was 77% and the mean ages of those with AD and caregivers were 80.2 and 78.2 years, respectively. The use of legal guardians was rare (4.3%), while the use of financial powers of attorney was more common (37.8%). Only 9.9% of these couples had discussed these issues with their doctor, whereas 47.9% expressed a need for it. Most factors associated with the use of these legal documents were related to the severity of dementia, such as suffering from dementia symptoms for more than three years, poor functioning, incontinence and behavioural symptoms. **Conclusions:** An obvious need exists for information on medico-legal issues related to dementia among caregivers of AD patients. When held soon after the diagnosis, such discussions could support the autonomy of these persons in spite of the AD and enable them to plan for the future in a way they themselves might desire.

17. EVALUATION OF THE CLINICAL FEATURES AND DIAGNOSTIC PROCESS IN THE PATHOLOGICAL SELECTION OF 28 FRONTOTEMPORAL LOBAR DEGENERATION WITH TAR DNA BINDING PROTEIN 43 CASES

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Backgrounds: TAR DNA binding protein 43 (TDP-43) is the most common pathological protein among frontotemporal lobar degeneration with TAR DNA binding protein 43 (FTLD-TDP). TDP-43 is suggested to be specific for FTLD-TDP and amyotrophic lateral sclerosis (ALS) cases, but it is also found occasionally in other neurodegenerative diseases. **Methods:** A comprehensive retrospective clinical symptom and diagnostic criteria evaluation of 28 FTLD-TDP autopsy cases. **Results:** The given clinical diagnoses and their frequencies among autopsy cases were frontotemporal dementia (FTD) 32,1%, Alzheimer's disease (AD) 28,6 %, combined FTD and ALS (FTD-ALS) 10,7 %, combined ALS-FTD 14,3 %, FTD-progressive aphasia (PA) 7,1 %, and psychosis 7,1 % as first part of combined diagnoses is the first clinical manifestation. The mean time from the onset of the symptoms to referral was 2,7±2,1 years (range 0,5-10 years). The onset of the disease was 61,3±13,7 (31 to 87) years, the referral age was 64,0±14,1 years, age of death was 68,4± 14years, and the mean time to mutism was 4,0±2,6 years (23 out of 28 subjects). The onset occurred in 82 % of subjects before the age of 70 years. The duration of the disease was interpreted short (≤5 years) in 13 out of 28 patients (46,4 %), and long (≥10 years) in 8 out of 28 patients (28,5 %), and nobody showed over 14 years disease. The initial reference was to psychiatrist in 54,6 %, and neurologist in 39,3 %. Seven cases out of 28 (25%) had compulsory psychiatric treatment at early phase of the disease. The history of dementia or ALS was positive in 15 out of 20 cases (53,6 %), and ten of those had two or more family members affected. The clinical diagnostic criteria for FTLD forms fulfilled (Neary et al 1998). **Conclusions:** TDP-43 pathology is related to progressive, severe clinical syndromes of FTLD with familial clustering in a half of cases.

18. HISTOLOGICAL DEFINITION OF VARIOUS HIPPOCAMPAL LESIONS AND THEIR APPLICABILITY

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Introduction: The hippocampal formation is one of most vulnerable brain regions, and thus its alterations are presumably common. Nevertheless, detailed histological definitions of pathological alterations are lacking. Consequently, the incidence of hippocampal lesions in the aged population, are lacking. **Methods:** The HE stained sections of posterior hippocampal formation were screened in 1388 consecutive autopsies obtained during a period of 10 years. All pathological lesions were sought and detailed histological definitions of various types of lesions were designed based on the pattern of cell loss and changes in the neuropil. **Results:** Overall a pathological alteration was found in 361 (26%) of all cases. In 251 cases the quality of the section was sufficient for the second part of this study, i.e. assessment of the inter-rater agreement while three experts assessed and assigned the lesion following the newly designed definitions. **Conclusions:** Hippocampal alterations are seen in conditions such as epilepsy, frontotemporal lobar degeneration and other neurodegenerative diseases and thus clear, simple and reproducible definitions of various alterations are needed. Here we have assessed the incidence of various lesions in an aged population, designed simple definitions and assessed the inter-rater agreement between three invited experts while applying the newly designed definitions.

19. STATINS AND DEMENTIA PREVENTION: A POPULATION-BASED STUDY (FINRISK)

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Background: The study aims to investigate statin use and dementia development in a Finnish population. **Methods**: FINRISK is a large population-based survey of cardiovascular risk factors carried out since 1972 every 5 years using independent, random and representative population samples from different parts of Finland. Several cohorts were part of the WHO-MONICA study. Data from cohorts 1972-1992 was linked to the Hospital Discharge Registry and Drug Reimbursement Registry (1995-2007) to ascertain dementia diagnoses and statins use. Only persons who were alive, without dementia and ≥65 years old in 1995 (when statins became available in Finland) were included. Cox regression analysis was used to investigate the statins-dementia relation. **Results:** 14294 persons were selected (mean education (SD) 6.6 (3.1) years; mean age (SD) in 1995 was 71.8 (4.9) years; 7681 (53.7%) were females). 1301 subjects developed dementia between 1995-2007; 3392 received statins (there was at least 1 year between drug prescription and dementia diagnosis). Statin use was associated with decreased risk of dementia: HR (95%CI) 0.78 (0.67-0.91) (controlled for age, sex, education, blood pressure, BMI, cholesterol). **Conclusions:** Statins seem to have a beneficial effect in dementia prevention, and this effect is partly independent of their cholesterol-lowering effect.

20. CARPATHIANS MOUNTAINS HERBAL FORMULA MAY PREVENT DESTRUCTIVE SEQUENCE OF AD

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Background: There is an immense amount of research taking place into new drug treatments for Alzheimer's disease (AD) and the other dementias. Recent research suggests that maintaining good overall health habits may help lower the chances of developing AD. **Methods:** It is clinically proved that high altitudes are conducive to the growth of numerous medicinal herbs that are the foundation for the area's indigenous systems of medicine. Several herbs are often used together to enhance effectiveness and synergistic actions and to reduce toxicity, stimulates of cell regeneration and vivifies the whole organism. **Results:** MOUNTAINS HERBAL TEA is a Carpathians Mountains herbal formula that consists of 10 different herbs and is another type of natural health option which we should all have the possibility to use for health and healing if we wish. This Mountains herbal formula is a sophisticated mixture of the most powerful and exotic mountains herbs to revitalize and activate the immune system to treat the symptoms of moderate to severe AD. This Mountains herbal tea is developed in Mountains Carpathians region. The health benefits of natural medicines and therapies basically largely dependant from the supply ecologically of pure uncontaminated ingredients. This herbal tea consists of 100% all-natural ingredients, with no chemically generated compounds and has zero negative side effects to correct the imbalance caused by AD disorders and strengthen the body appropriately so that its natural defense mechanism can work effectively to control AD disorders and build resistance against it. **Conclusions:** AD is characterized by loss and/or atrophy of neurons in discrete regions of the brain, and that is accompanied by extracellular proteolysis and deposits of beta-amyloid and the intracellular accumulation of neurofibrillary tangles. Bucovinian Mountains herbal formula may prevent this destructive sequence by adjusting the activity of extracellular proteolysis. A program of early diagnostic biological tests establishes the extent to which the body has aged and also supervises process of developing AD.

21. ADIPOSITY AND DEMENTIA OVER 32 YEARS IN SWEDEN

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Background Overweight and obesity measured during both mid- and late-life has been related to higher risk for late-life dementia. However, some studies have shown no such relationship, and instead have reported on a late-life decline in body mass index or body weight that appears to be due to the underlying pathology of the disorder. Differences in study designs vary and may contribute to differences in reported findings. Using a 32 year longitudinal population-based study in Gothenburg, Sweden, we evaluated overweight and obesity in relationship to dementia in three ways that mimicked reported study designs.
Methods The relationship between dementia and obesity was evaluated in a representative cohort of 1462 nondemented Swedish women who were followed from ages 38-60 years for 32 years, using neuropsychiatric, anthropometric, clinical, and other measurements. The relationships between body mass index, waist circumference and waist-to-hip ratio and dementia were evaluated using Cox proportional hazards regression analyses of all individuals who became demented over the 32 year follow-up period; and logistic regression analyses using baseline data in relationship to dementia only among those participating 32 years, and examined in both 1968 and 2000-03.
Results Our data suggest that a high WHR at mid-life is a risk factor for dementia among women who survive to at least age 70 and participate in a follow-up exam. No effect of BMI was observed. WHR is highly predictive of mortality before age 70, which may be a reason why using Cox proportional hazards models this association is not observed.
Conclusions Our data suggest that a high WHR at mid-life is a risk factor for dementia among women who survive to at least age 70 and participate in a longitudinal follow-up. This has profound mid-life implications for dementia prevention, and for considerations related to the identification of risk factors for diseases of high age.

22. CHALLENGING COUPLE RELATIONS IN MIDLIFE MAY BENEFIT LATE-LIFE COGNITIVE HEALTH

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Background: Although social networks and activities have recently been suggested to protect against dementia, few studies exist on the relevance of living in a couple relation as compared to being single, divorced or widowed. The purpose of this study was to evaluate this relevance, including the quality of the marital relation, for late-life cognitive function. **Methods:** A prospective population study design with 1449 participants and a 21-year follow-up was used. The main statistical method was logistic regression with adjustments for several physiological and life-style factors at midlife and also for ApoE and age at follow-up. **Results:** Persons living with a partner in midlife were significantly less likely to show cognitive impairment compared to non-cohabitants. The highest risk was found for those widowed in midlife and still so at the follow-up with almost an eight-fold risk increase for Alzheimers disease. Within the cohabitant group, a higher risk for late-life cognitive impairment was found for those who at midlife said they had no problems with spouse and/or children. Within the group of singles, loneliness was a more critical risk factor than for any other group. **Conclusions:** Living in a partner relation where challenges are common may be beneficial for long-term cognitive health. Socio-emotional factors behind Alzheimers disease are suggested by the specific risk increase for widowed in relation to singles, and also by the indicated critical role of friendship relations for singles.

23. VISUAL ASSESSMENT OF [^{11}C]PIB PET IN PATIENTS WITH COGNITIVE IMPAIRMENT

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Background: The purpose of the study was to evaluate the visual assessment of N-[methyl-11C]2-(4'-methylaminophenyl)-6-hydroxy-benzothiazole ([^{11}C]PIB), which is a positron emission tomography tracer, images in clinical patient population. **Methods:** We compared the visual ratings of two readers using kappa statistics and correlated the results of visual and quantitative region-of-interest (ROI) analyses. The sensitivity and specificity of the visual assessment was determined using quantitative data from previously scanned 18 healthy controls: [^{11}C]PIB uptake was considered as abnormal if it was more than +2 SD of mean of the healthy subjects. **Results:** The evaluation of visual classification as "normal" or "abnormal" showed good interobserver agreement (κ=0.90). There was a clear correlation between visual and quantitative analysis (r= 0.47–0.79, $p<0.001$). The most difficult visually assessed brain area was the putamen (κ =0.11; correlation with quantitative analysis: reader A r=0.22; reader B r=0.60). **Conclusions:** Our study shows that visual evaluation of [^{11}C]PIB images conforms with quantitative analyses also in a clinical patient population supporting the feasibility of visual evaluation in clinical settings.

24. 3D PATTERNS OF GREY MATTER ATROPHY ON SERIAL MRI SCANS PRECEDING THE PROGRESSION FROM MILD COGNITIVE IMPAIRMENT TO ALZHEIMER'S DISEASE

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Background: Morphometric brain abnormalities are potential biomarkers for Alzheimer's disease (AD). The aim of this study was to assess the progression of grey matter loss on serial brain MRI scans of mild cognitive impairment (MCI) subjects. **Methods:** 63 MCI subjects (15 converted to AD) with 3 serial MRI scans (1 year scan interval) were selected from the MR database at the Kuopio University Hospital. Voxel-base morphometry (VBM) under SPM5 was used for comparing the changes in grey matter in a longitudinal approach. The images were segmented and normalized using the unified segmentation model and smoothed with a 12 mm Gaussian kernel. **Results**: We found significant differences in grey matter in the parahippocampal gyrus in the MCI subjects which subsequently progressed to AD already at baseline. The location of the cluster was stable longitudinally, and increased in size at subsequent timepoints. By the time that subjects had a clinical diagnosis of AD, the pattern of grey matter loss had become more widespread, and also involved the superior temporal gyrus. **Conclusions**: This progressive pattern of the changes suggests that the earliest changes in MCI subjects involving the middle temporal lobe are detectable at least 2 years before establishing the diagnosis of AD. Moreover, the 3D atrophy patterns could help identifying the MCI subjects prone to progress to AD.

25. PHARMACOKINETIC PROPERTIES OF A NOVEL PET TRACER FOR IMAGING BRAIN Aβ

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Background: A novel PET-tracer for amyloid imaging, ^{18}F-labeled Pittsburgh compound B ([^{18}F]PIB), has recently been synthesized in Turku PET Centre (TPC). We wanted to evaluate the pharmacokinetic properties of [^{18}F]PIB using healthy Sprague Dawley rats and compare them with those of [^{11}C]PIB to further estimate the suitability of [^{18}F]PIB for clinical assessment of beta-amyloid burden in the brain. **Methods:** Biodistribution of [^{11}C]PIB and [^{18}F]PIB was evaluated with classic autoradiographic methods and both *ex vivo* and *in vivo* PET imaging. Metabolism and binding to plasma proteins were studied with radio-TLC and ultracentrifugation, respectively. Radiation dosimetry estimates were based on the obtained biodistribution data. **Results:** The pharmacokinetic profile of [^{18}F]PIB resembles that of [^{11}C]PIB. Both tracers successfully crossed the blood-brain-barrier and the clearance of free and non-specifically bound tracer from the brain was relatively fast. However, [^{18}F]PIB showed slightly slower clearance from the brain, especially from the white matter containing structures. Both tracers were rapidly metabolized to numerous polar metabolites and largely bound to plasma proteins. Except for the excreting organs, no significant uptake was observed in the peripheral tissues. No radioactivity was detected in bone. Effective dose estimates of [^{11}C]PIB and [^{18}F]PIB are approvable. **Conclusions:** Based on its pharmacological profile, [^{18}F]PIB shows potential as a novel tracer for PET-imaging of brain Aβ.

26. PREDICTAD – FROM PATIENT DATA TO PERSONALISED HEALTHCARE IN ALZHEIMER'S DISEASE

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Background: When new drugs or prevention strategies become available for Alzheimer's disease, early detection, even pre-symptomatic, of the disease will become essential in selecting patients for treatment. Today there is no single test can predict whether a particular person will develop the disease. The goal of the PredictAD EU-project is to provide a standardised and objective software solution for enabling earlier diagnoses of AD, improved monitoring of treatment efficacy, and improved cost-effectiveness of diagnostic protocols. **Methods:** Heterogeneous data including neuropsychological test scores, MRI imaging, PET (FDG/PIB) imaging, TMS/EEG and biomarkers detected from blood (metabolomic, proteomic) will be integrated to identify an efficient combination of markers. The project has three main parts: 1) implementation of methods for quantifying data, 2) construction of statistical models based on numerous biomarkers, and implementation of a software solution implemented, and 3) validation of accuracy and usability of the solution. **Results:** Tools for the quantification of data are developed and quantification of four patient cohorts is ongoing. Application specifications have been carefully defined and the first prototype version is actively developed. **Conclusions:** PredictAD may enable doctors to provide medical care at an earlier stage, at a time when clinical diagnosis using only signs and symptoms of disease is challenging.

27. INCREASED AMYLOID DEPOSITION DETECTED BY [11C]PIB IN MEDIAL TEMPORAL CORTEX OF ALZHEIMER PATIENTS WHEN PARTIAL VOLUME EFFECT IS TAKEN INTO ACCOUNT

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Background: [^{11}C]PIB is a PET radioligand for quantifying amyloid deposition in human brain. In Alzheimer's disease (AD) [^{11}C]PIB uptake is increased especially in frontal cortex (FCX) and posterior cingulate (PC), but previous studies have not detected significant increase in medial temporal lobe (MTL). We hypothesized this to be due to gray matter atrophy in AD, which causes more pronounced partial volume effect (PVE) in patients compared to controls. In post-mortem studies amyloid deposition in MTL has been observed early in the course of AD. **Methods:** We scanned 20 patients with probable AD and 12 healthy elderly controls with [^{11}C]PIB and T1-MRI. PVE correction (PVEc) was calculated with both a conservative method (M-PVEc) to avoid possible over-correction and a more radical method (mMG-PVEc). **Results:** In the non-PVEc images the increase of [^{11}C]PIB uptake in MTL in AD compared to healthy controls was 5.1 ± 14.4 % ($p=0.135$), whereas in the M-PVEc images the uptake was increased by 17.3 ± 14.4 % ($p < 0.001$) and in the mMG-PVEc images by 16.8 ± 14.0 % ($p < 0.001$). In AD patients the [^{11}C]PIB uptake in MTL correlated with uptake in FCX only in mMG-PVEc images ($r = 0.45$, $p = 0.047$); no significant correlations between [^{11}C]PIB uptake in PC and MTL were observed. **Conclusions:** When [^{11}C]PIB images are corrected for PVE, increased amyloid deposition in AD is detectable with this method in human brain *in vivo* also in the MTL.

28. TWO-YEAR FOLLOW-UP OF [^{11}C]PIB UPTAKE AND BRAIN VOLUME IN ALZHEIMER'S DISEASE PATIENTS AND AGED CONTROLS

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Background: The accumulation pattern of beta amyloid (Aβ) over time and its relationship with Alzheimer's disease (AD) severity are unclear. We investigated the brain uptake of the amyloid ligand [^{11}C]PIB (^{11}C-labeled Pittsburgh Imaging Compound B) over a two-year follow-up in AD patients and healthy controls. **Methods:** 14 AD patients and 13 controls were examined at baseline and after two years with [^{11}C]PIB positron emission tomography (PET), magnetic resonance imaging (MRI) and neuropsychological assessments. [^{11}C]PIB uptake was analyzed with a voxel-based statistical method (SPM) and quantitative data were obtained with automated region-of-interest analysis. MRI data were analyzed with voxel-wise tensor-based morphometry.**Results:** AD patients had increased [^{11}C]PIB uptake versus controls at both time points. At group level, the AD patients' [^{11}C]PIB uptake did not increase significantly in any brain region during follow-up. MRI showed progressive brain volume changes in the AD patients e.g. in the hippocampal region, the temporal cortex, the precuneus and the ventricles. The mean MMSE score of the AD patients declined from 24.3 (SD 3.1) to 21.6 (SD 3.9) during follow-up. Cognitive decline was also evident in other neuropsychological tests. **Conclusions:** AD patients did not show increased [^{11}C]PIB uptake during two-year follow-up although disease progression was evident according to volumetric MRI and neuropsychological assessments.

29. PET AMYLOID LIGAND [11C]PIB UPTAKE AND CEREBROSPINAL FLUID B-AMYLOID IN MILD COGNITIVE IMPAIRMENT

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Background: In mild cognitive impairment (MCI), Alzheimer`s disease (AD)-type cerebrospinal fluid (CSF) biomarker profiles predict rapid progression and conversion to AD. An increased brain amyloid burden in AD and MCI has been demonstrated with PET using [11C]PIB (Pittsburgh compound B). Little is known about the relationship between these biomarkers in MCI. **Methods**: We studied 15 patients with amnestic MCI and 22 controls with PET using [11C]PIB. In MCI patients, CSF levels of Aβ42, pTAU, totalTAU and the Aβ42/pTAU ratio were measured. **Results**: In MCI patients, CSF Aβ42 was abnormal in 53% of patients, total TAU in 67%, pTAU in 64% and the Aβ42/pTAU ratio in 64%. A composite neocortical [11C]PIB uptake score was increased in 87% of the MCI patients. Only 54% of [11C]PIB-positive subjects showed AD-type Aβ42values. During a 2-year follow-up, 6 MCI patients converted to AD, all of them had increased neocortical PIB scores at the MCI stage. Abnormal CSF Aβ42 was found in 3 patients, pTAU in 3 patients and Aβ42/pTAU ratio in 4 patients. **Conclusion**: Follow-up studies are needed to confirm whether [11C]PIB uptake might be more sensitive than CSF Aβ42 concentration in detecting amyloid burden in MCI, as suggested by the results of this study.

30. CORTICAL THICKNESS ANALYSIS TO DETECT PROGRESSIVE MILD COGNITIVE IMPAIRMENT — A REFERENCE TO ALZHEIMER'S DISEASE

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Background: Subjects with mild cognitive impairment (MCI) have a markedly increased risk of developing dementia, particularly Alzheimer's disease (AD). MCI is, however, a heterogeneous condition. Distinguishing characteristics of the MCI subjects who have a high probability to progress to clinical AD would have a great impact on monitoring the disease development and treatment planning. **Methods:** We assessed the baseline MRI and 5-year clinical follow-up of 60 MCI subjects (mean age $\pm$ S.D.: 72.2 $\pm$ 5.0 years) in order to investigate differences in cortical thickness between the progressive (P-MCI) and stable (S-MCI) MCI subjects. Cortical thickness was measured in the baseline T_1-weighted structural MR images using an automatic computational surface-based method. **Results:** 15 MCI subjects converted to AD on average 1.9 $\pm$ 1.3 years after the baseline examination, while the status of 45 MCI subjects remained stable. At the baseline, the P-MCI group had significantly ($p < 0.05$) reduced cortical thickness in bilateral areas of superior and middle frontal gyri, superior temporal sulci, middle and inferior temporal and fusiform gyri as well as in parahippocampal, cingulate, retrosplenial and right precuneal and paracentral cortices compared to the S-MCI-group. **Conclusions:** Our results suggest that cortical thickness analysis could be used to detect subjects with progressive form of MCI few years before they convert to clinical AD.

31. ENTORHINAL VOLUMETRY EXCEEDS HIPPOCAMPAL FMRI BY DISCRIMINATING ACCURACY IN MILD COGNITIVE IMPAIRMENT

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Background: The discriminating power of potential structural and functional magnetic resonance imaging (MRI) markers of prodromal Alzheimer's disease (AD) was investigated in this study. **Methods:** Structural MRI and functional MRI (fMRI) during encoding and cued retrieval of word-picture pairs were performed in 21 elderly controls, 14 subjects with mild cognitive impairment (MCI), and 15 mild AD patients. The volumes of the hippocampus and entorhinal cortex were manually outlined. The extent of hippocampal activation was extracted using SPM2. Discriminant analyses were conducted in SPSS. **Results:** Entorhinal volumes were significantly smaller in MCI compared to controls ($p<0.001$). Both entorhinal and hippocampal volumes showed greater atrophy in AD compared to MCI ($p<0.002$ and $p<0.02$). During encoding and retrieval, the largest extent of hippocampal fMRI activation was observed in controls and the smallest in AD. The entorhinal volume was the best, and delayed recall of the wordlist the second best discriminator with accuracies ranging from 85.7% to 97.2% and from 75% to 93.5% between the groups. The discriminating accuracy of hippocampal volume ranged from 42.9% to 69.4% and that of hippocampal encoding or retrieval fMRI activation from 41.4% to 57.7% between the groups. **Conclusions:** Assessment of entorhinal atrophy seems promising in the identification of AD at its early stages, whereas hippocampal volumetry and fMRI were less accurate markers of prodromal AD in this study.

32. REDUCED MEDIAL TEMPORAL REPETITION SUPPRESSION IS RELATED TO IMPAIRED MEMORY ENCODING

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Background: Suppression of medial temporal lobe (MTL) activity to repeatedly viewed stimuli has been suggested as a marker of successful recognition of familiarity in healthy young subjects. Repetition suppression is known to be impaired in patients with Alzheimer's disease (AD), who characteristically have significant MTL pathology and difficulty learning new information. **Methods:** In this functional magnetic resonance imaging (fMRI) study, we investigated the relationship between MTL activity during processing Repeated face-name pairs and memory performance in 90 individuals ranging from healthy young (n=15) to cognitively normal (Clinical Dementia Rating, CDR=0.0; n=30) and mildly impaired (CDR=0.5; n=30) elderly and AD patients (CDR=1.0; n=15). All subjects underwent a post-scan associative name recognition memory test and a subset of the elderly subjects (n = 60) additional neuropsychological testing of verbal memory. **Results:** The left anterior MTL activity during Repeated stimuli was inversely related to performance on the post-scan recognition for the recently studied face-name pairs ($r=-0.62$, $p<0.001$). Similarly, greater MTL Repeated activity was correlated with worse word-list delayed recall performance ($r=-0.61$, $p<0.001$). **Conclusions:** Our findings suggest that MTL response suppression to previously encountered information is related to successful memory formation for novel information as measured by delayed recognition and recall. Difficulty to discriminate familiar from novel information may be a sensitive marker of MTL dysfunction related to prodromal AD.

33. COMBINATION ANALYSIS OF NEUROPSYCHOLOGICAL TESTS AND STRUCTURAL MRI MEASURES IN DIFFERENTIATING AD, MCI AND CONTROL GROUPS – THE ADDNEUROMED STUDY

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Background: To study the ability of neuropsychological tests, manual hippocampal measurement, automated cortical thickness measurement, and automated MRI volume measurement, alone and in combination, to identify subjects with Alzheimer's disease (AD), mild cognitive impairment (MCI), and healthy age-matched controls. **Methods:** 120 AD patients, 120 MCI subjects, and 111 controls were selected from the AddNeuroMed database. Neuropsychological tests were assessed in each subject. Manual hippocampal volume, automated cortical thickness and volume measurements were performed on high resolution T1 weighted images. **Results**: The cortical thickness and volumes in MCI subjects were significantly decreased in limbic/paralimbic areas and temporal lobe compared to controls. Atrophy was much more extensive in the AD patients compared to MCI subjects and controls. Neuropsychological tests alone revealed the highest accuracy in differentiating AD from MCI (78%) or controls (92%), and differentiating MCI from controls (79%) compared to cortical thickness or volume measurement alone. The combination of neuropsychological tests and volumes revealed the highest accuracy (84% AD vs. MCI; 95% AD vs. control; 83% MCI vs. control). Adding cortical thicknesses into analysis did not improve accuracy. **Conclusion**: A combination of neuropsychological tests and MR volumes are important when discriminating AD from healthy controls and MCI.

34. VOXEL-BASED ANALYSIS OF CEREBRAL GLUCOSE METABOLISM IN MONO- AND DIZYGOTIC TWINS DISCORDANT FOR ALZHEIMER'S DISEASE

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Background: As sporadic Alzheimer's disease (AD) is a multifactorial disease twin pairs are useful in studying its pathogenesis and etiology. Cerebral glucose metabolism is reduced in AD patients with relative sparing of the primary motor and sensory cortices. We studied cerebral glucose metabolism in seven monozygotic (MZ) and nine same-sexed dizygotic (DZ) twin pairs discordant for AD using positron emission tomography (PET). **Methods:** The inclusion of MZ and DZ twins enabled evaluation of the possible genetic vs. environmental contribution to glucose metabolism and susceptibility to develop AD. The analysis was made utilizing modern voxel-based analysis methodology statistical parametric mapping without a priori hypothesis about the locations of possible differences. To obtain quantification of regional glucose metabolism, an automated ROI analysis was performed. **Results:** We found the cerebral glucose metabolism to be reduced in the demented co-twins compared to controls in cerebral regions affected by AD. Also the non-demented MZ co-twins showed reductions in glucose metabolism in parietal, lateral temporal and medial temporal cortices as well as in putamen. In contrast, no reductions in cerebral GMR were found in the non-demented DZ co-twins. **Conclusions:** The reductions in non-demented MZ co-twins are possibly early indicators of the disease process before onset of clinical dementia or are genetic markers of susceptibility to AD. As MZ twins have all genes in common, whereas DZ twins share on average half of their segregating genes, the difference between non-demented MZ and DZ co-twins may be due to genetic differences.

35. FMRI RESPONSE TO RIVASTIGMINE IN ALZHEIMER'S DISEASE

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Background: The effect of acetylcholinesterase inhibitors (AChEI), which are current therapies for Alzheimer´s Disease (AD), can be examined using functional MRI (fMRI). Previous fMRI studies have shown both AChEI induced increases and decreases in brain activations in AD. Increased activation can be explained by enhanced processing while decreased activation may be caused by cholinergic stimulation restoring attentional competence, resulting in a lesser need for compensative hyperactivation. Objective: To investigate whether cholinergic stimulation induced fMRI activation changes are related to baseline activation (reflecting already recruited compensatory resources) and cognitive status of mild AD patients. **Methods:** Twenty mild AD patients underwent structural MRI and fMRI during a face recognition task after a single oral dose of placebo, single oral dose of rivastigmine (acute) and one month oral treatment with rivastigmine (chronic). Functional data analysis was performed using SPM5 with cluster-corrected threshold $p < 0.05$ for statistical significance. **Results:** AD patients showed significantly more activation under chronic than placebo exposure. The signal intensity difference in the prefrontal cortex between chronic and placebo treatments were significantly correlated with neuropsychological test results. The ten cognitively more impaired AD patients displayed increased, while the ten less impaired patients exhibited decreased prefrontal activity during both the acute and chronic cholinergic stimulation when compared to placebo. **Conclusions:** This study demonstrates that mild AD is a heterogeneous state, in which the response to AChEIs may be associated with the level of attentional dysfunction and compensatory mechanisms recruited at baseline.

36. LOCALIZATION OF IL-18 BINDING PROTEIN, IL-18 RECEPTOR, AND IL-1 RECEPTOR II IN THE BRAIN OF ALZHEIMER'S DISEASE PATIENTS

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Background: The neuropathological findings of Alzheimer's disease patients includes Amyloid-beta (Aβ) plaques, neurofibrillary tangles composed of microtubule binding protein tau, and neuroinflammation. The reasons why Aβ accumulates in the brain and forms insoluble plaques, and why it is not removed and degraded by microglia or astrocytes are not fully understood. Soluble non-signalling cytokine binding-proteins, including Interleukin-18 binding-protein (IL-8BP) and Interleukin-1 receptor-II (IL-1RII) may have importance in masking the developing plaque unrecognizable to the neural cells for the removal. **Methods:** We carried out immunohistochemical stainings on brain samples obtained from subjects with AD related lesions to localize IL-18BP and IL-1RII. Localization of signalling Interleukin-18 receptor (IL-18R) was also assessed. **Results:** IL-18BP was mainly detected in blood vessels and neurons. Granules were detected also in astrocytes and microglia. IL-1RII was found especially in neurons and in myelin, but also in other glial cells as well as diffuse neuropil staining. However, we also detected IL-18BP and especially IL-1RII in plaques, suggesting their role in binding of IL-18 and IL-1, respectively, and inactivating them. IL-18R was detected especially in neurons and their dendrites, but it was also present in glial cells. Surprisingly some staining seemed to localize in plaques. **Conclusion:** IL-18BP and IL-1RII may have a role in masking Aβ as unrecognizable for the uptake from the extracellular space.

37. EFFECTS OF IL-18 ON HUMAN SH-SY5Y NEUROBLASTOMA CELL LINE

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Background: Neuropathological changes in Alzheimer´s disease (AD) include extracellular Amyloid-β plaques and intraneuronal neurofibrillary tangles composed of hyperphosphorylated tau-protein. There are also signs of chronic inflammation occurring in the brain. However, the mechanisms leading to neuronal cell death remains unresolved. Interleukin-18 (IL-18) is an inflammatory cytokine largely produced in the brain by activated microglia. IL-18 can enhance production of toxic inflammatory molecules such as Interferon-γ and Interleukin-1β. The link between IL-18 and pathogenesis of AD is not understood, but we have previously found that IL-18 can have impact on tau and kinases related to tau phosphorylation. In this study, our purpose was to find new changing targets in IL-18 treated cells compared to untreated cells. **Methods:** We studied the impact of IL-18 on protein profiles of differentiated human SH-SY5Y neuron-like cells in different time-points by using two-dimension difference-gel-electrophoresis. **Results:** The most changed protein profiles were found in 24h IL-18 treated cells, but also treatments for 48h and 72h showed alterations compared to untreated cells. The number of protein spots was the greatest in 48h. The proteins exhibiting changes will be identified later by mass spectrometry and database searches. **Conclusion:** IL-18 had time-related effects on protein expression of SH-SY5Y cells.

38. EFFECTS OF SELADIN-1 KNOCK-DOWN ON APP PROCESSING DURING APOPTOSIS

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Background: Alzheimer's disease (AD) is neuropathologically characterized by extracellular deposits of β-amyloid (Aβ), which is generated after sequential cleavage of amyloid precursor protein (APP) by β- and γ-secretases. Seladin-1 is a neuroprotective protein found to be selectively down-regulated in brain regions associated with AD. Seladin-1 is regulated in response to oxidative stimuli and it confers resistance against Aβ- and oxidative stress-induced apoptosis. Moreover, genetic studies have shown that *seladin-1* gene variants associate with AD. These data suggest that seladin-1 plays a pivotal role in the AD pathogenesis. **Methods:** Here we have studied the effects of seladin-1 knock-down on APP processing in both normal and apoptotic conditions. We selectively down-regulated seladin-1 steady-state levels using small interfering RNAs (siRNA) in SH-SY5Y human neuroblastoma cells over-expressing APP751 isoform and/or BACE1. Forty-eight hours after siRNA transfection, seladin-1 knock-down and control cells were treated with staurosporin (STS) to induce apoptosis. **Results:** Approximately 60 % reduction in seladin-1 protein levels increased APP C-terminal fragment (C83 and C99) levels an average 1.5-fold in normal conditions. Interestingly, STS-induced apoptosis increased caspase-3 activity an average two-fold in seladin-1 knock-down cells when compared to control cells. This resulted in increased BACE1-dependent APP cleavage as well as decreased GGA3 levels and subsequent augmentation of BACE1 levels. **Conclusions:** These findings suggest that down-regulation of seladin-1 levels may influence in AD pathogenesis.

39. OVER-EXPRESSION OF UBQLN1 AFFECTS APP MATURATION AND γ-SECRETASE ACTIVITY IN HUMAN NEUROBLASTOMA SH-SY5Y CELLS

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Background: Genetic studies have shown that ubiquilin-1 (UBQLN1) gene variants associate with Alzheimer's disease (AD). Moreover, modulation of UBQLN1 steady state levels affects the trafficking of amyloid precursor protein (APP), β-amyloid secretion, and γ-secretase complex component levels in different cell lines, suggesting that UBQLN1 plays an important role in the AD pathogenesis. **Methods:** Here we have assessed the effects of UBQLN1 over-expression on APP processing using human neuroblastoma SH-SY5Y cell line stably over-expressing APP751 isoform. **Results:** Transient over-expression of UBQLN1 transcript variant 1 (UBQLN1-TV1) significantly enhanced APP maturation, increased APP C-terminal fragments (C83 and C99) and increased APP intracellular domain (AICD) levels. Moreover, when UBQLN1-TV1 was co-expressed with another γ-secretase substrate, leukocyte common antigen related protein (LAR), we observed a similar increase in LAR intracellular domain (LICD). However, AICD generation was not increased in the co-expression situation, pointing to a competition mechanism in which γ-secretase prefers LAR to APP. **Conclusions:** These findings indicate that UBQLN1 over-expression not only enhances APP maturation, but also increases γ-secretase activity in SH-SY5Y cells.

40. THE NOVEL ALZHEIMER'S DISEASE-ASSOCIATED PROTEIN UBIQUILIN-1 REGULATES PRESENILIN-1 AGGREGATION AND FORMATION OF AGGRESOMES

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Background: The ubiquitin-like protein ubiquilin-1 is genetically and functionally associated to Alzheimer's disease (AD) and it regulates proteasomal degradation of proteins including AD-associated presenilin-1 (PS1). Ubiquilin-1 may also play a role in other neurodegenerative diseases involving abnormal protein aggregation. **Methods:** Here we characterized the role of ubiquilin-1 transcript variants (TV) in protein aggregation and ubiquitin-proteasome system (UPS) in HEK293 cells. **Results:** We found that full-length ubiquilin-1 TV1 and TV3, which lacks the proteasome interaction domain, induced accumulation and aggregation of high-molecular-weight PS1 fragments. Additionally, formation of aggresome-like structures significantly increased in cells overexpressing PS1 and TV1 or TV3 as compared to control cells. These effects were most prominent in TV3-expressing cells. Both the proteins co-localized in the aggresomes. Moreover, characteristic of aggresomes, the intermediate filament protein vimentin redistributed to the aggresomal structures. Overexpression of TV1 or TV3 did not cause a general impairment of the UPS. **Conclusions:** Collectively, our results suggest that ubiquilin-1 regulates PS1 aggregation and aggresome formation, which may partially contribute to AD pathogenesis.

41. CEREBRAL GLUCOSE AND OXYGEN METABOLISM IN PATIENTS WITH M.3243A>G MUTATION IN MITOCHONDRIAL DNA

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Background: The m.3243A>G mutation is the most common cause of mitochondrial disease leading to decreased oxygen and increased glucose consumption *in vitro*. We aimed to quantify the oxygen and glucose metabolism in the brain of patients with this mutation. **Methods:** 14 patients, asymptomatic (absence of diabetes and cerebral symptoms, n=5) and symptomatic (n=9) and 14 controls underwent PET and 2- [^{18}F]fluoro-2-deoxyglucose, [^{15}O]O_2 and [^{15}O]H_2O as the tracers. White-matter changes and atrophy in the brain were assessed using MRI. **Results:** Oxygen metabolism in the brain was significantly lower in the patients than that in the controls. The decrease was 21 - 33% in cortical regions, putamen, thalamus and cerebellum. Oxygen to glucose consumption ratio was also significantly reduced in frontal cortex, putamen, thalamus and cerebellum of the patients. Glucose uptake was significantly decreased in the putamen, thalamus, occipital and parietal cortices only in the symptomatic patients. No differences in blood flow were detected. In MRI only the degree of cerebellar atrophy in the symptomatic patients group differentiated the patients from the controls. **Conclusions:** Decreased cerebral oxygen metabolism characterizes patients with the m.3243A>G mutation also in brain areas where no abnormalities in glucose metabolism, blood flow or MRI are detected.

42. MUTATIONS IN *CHMP2B* ARE NOT A CAUSE OF DEMENTIA IN FINNISH PATIENTS WITH FTLD

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Background: Frontotemporal lobar degeneration (FTLD) is a genetically complex disorder. Mutations in the microtubule-associated protein tau (*MAPT*) gene and the progranulin (*PGRN*) gene have been found to be a common cause of familial FTLD.[1] However, we haven't found any mutations in *MAPT* and *PGRN* in Finnish patients with FTLD.[2,3] Mutations in the charged multivesicular body protein 2B (*CHMP2B*) gene have been recently associated with FTLD in a few families.[1] Our aim was to investigate *CHMP2B* mutations in a clinical series of patients with FTLD in Northern Finland.
Methods: *CHMP2B* exons 1-6 were sequenced from 72 patients with FTLD. Mutations in *MAPT* and *PGRN* were excluded from these patients. **Results:** No pathogenic *CHMP2B* mutations were identified in the cohort. Three previously reported polymorphisms were detected also in Finnish patients with FTLD. **Conclusions:** Our results confirm that mutations in *CHMP2B* are a rare cause of FTLD.

43. COMBINED RISK EFFECTS OF *IDE* AND *NEP* GENE VARIANTS ON ALZHEIMER'S DISEASE ADDITIVELY INCREASE THE SUSCEPTIBILITY TO DISEASE

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Background: Candidate gene-based association studies with the *Insulin degrading enzyme (IDE)* and *Neprilysin (NEP)* genes in a large clinic-based series of AD and control subjects originating from Finland suggest that *IDE* and *NEP* are risk genes for AD. In addition to *APOE*, *NEP* and *IDE* genes show the strongest risk effect on AD among this population. It has been recently suggested that combining the information on variants of multiple genes may give a better idea of AD susceptibility. **Methods:** Based on genetic findings and the fact that both IDE and NEP contribute to Aβ degradation, we investigated whether combining the information on risk variants of *IDE* and *NEP* genes could additively modify the risk of AD. **Results:** Interestingly, a combination of risk genotypes for *IDE* and *NEP* genes leads to even higher risk of AD when compared to individual risk gene effects of *IDE* and *NEP*. Individuals carrying the risk genotypes in both genes had significantly increased susceptibility to AD (~3-fold) when compared to individuals without these genotypes. Combination of risk genotypes for *NEP* and *IDE* genes leads also to slightly decreased cerebrospinal fluid Aβ42 levels. Additionally, we found that age-at-onset for risk-allele carriers of two *IDE* SNPs was significantly lower in AD patients when compared to non-carriers. In summary, this study provides evidence for additive risk effect for *IDE* and *NEP* genes on AD. Furthermore, it suggests that risk-allele carriers of *IDE* show lower disease onset age. **Conclusions:** These findings warrant for further studies concerning IDE and NEP in the context of AD.

44. LOCI AND GENES CONFERRING AN INCREASED GENETIC RISK IN FINNISH ALZHEIMER'S DISEASE COHORT

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Background: Late-onset Alzheimer's disease (LOAD) is a complex disorder, whose risk is influenced by both genetic and environmental factors. It is likely that the overall genetic susceptibility for LOAD is affected by multiple risk factors with small individual risk effects, but their identification has proved to be a challenging task. **Methods:** Here we describe genetic case-control association studies for LOAD in Finnish population, where the AD patients and controls (at present 550 cases and 650 controls) derived from a geographically restricted area in eastern Finland build up a unique homogeneous study population. **Results:** We carried out genome-wide linkage disequilibrium (LD) mapping aiming at finding novel risk loci for LOAD. Eight chromosomal loci were associated with AD with more than one microsatellite marker (1p36.12, 2p22.2, 3q28, 4p13, 10p13, 13q12, 18q12.1 and 19p13.3). The plausible candidate genes in close proximity to these loci found in LD mapping study and other genes which have a biological relevance to AD provided targets for genetic association studies. We investigated a myriad of genes (e.g. APOD, PGC1, SIRT1, LDLR, SST, APOE, NCSTN, BCHE-K) related to beta-amyloid degradation, cholesterol metabolism and diabetes using traditional statistical analyses. Polymorphisms in genes such as neprilysin, IDE or CYP46 showed significant association with AD in the whole study cohort, particularly emphasising the role of beta-amyloid degrading enzymes in further studies. **Conclusions:** Although a number of additional disease-associated loci have been identified, the ε4 allele of apolipoprotein E (*APOE*) gene remains the only thus far well established genetic risk factor for LOAD.

45. ALTERED INGESTIVE BEHAVIOUR & CORE BODY TEMPERATURE IN THE TRIPLE TRANSGENIC 3XTGAD MICE

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Background: Alterations in energy balance such as changes in body weight, and food intake are frequently observed throughout the progression of Alzheimer's disease (AD) in humans. We have previously demonstrated an altered energy balance in triple transgenic (3xTgAD) mice, which overexpress human amyloid precursor protein, presenilin-1 and tau, and develop AD-like behavioural deficits and age-dependant Aβ plaque pathology and neurofibrillary tangles. These mice display altered body weight, food intake and metabolic rate. To further characterise these changes in energy balance we examined the ingestive behaviour and body temperature of 3xTgAD mice. **Methods**: The behavioural satiety sequence (BSS) test was used to examine ingestive behaviour. Individually housed 6-month old 3xTgAD and non-transgenic (Non-Tg) control mice were fasted overnight, and after food was returned behaviour was monitored every 30 s for 2h. In a separate experiment core body temperature was monitored by remote radiotelemetry for seven days. **Results**: In response to a fast 3xTgAD mice spent significantly more time eating and drinking, and less time grooming when compared to Non-Tg controls. No difference in activity or resting was observed between groups. 3xTgAD mice also ate significantly more food than Non-Tg controls. In a separate experiment, core body temperature was elevated over a 24h period in 3xTgAD mice. **Conclusions**: These preliminary data demonstrate altered ingestive behaviour and core body temperature in 3xTgAD mice, although the relevance of these findings to human AD remains to be tested.

46. EFFECTS OF HUMAN INTRAVENOUS IMMUNOGLOBULIN ON BETA-AMYLOID IN PRECLINICAL MODELS

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Background: Human intravenous immunoglobulin (hIVIG) is an established and well-tolerated treatment for many neurological conditions. Recent data suggest that it also included anti-beta-amyloid (Abeta) antibodies. Present study aims at developing methods for assessing the effects of hIVIG on neutralization and degradation of harmful Abeta species. **Methods:** Toxicity in primary hippocampal cultures, degradation of amyloid plaques by microglia in ex vivo assay using brain sections from APP/PS1 transgenic mice, passive immunization of APP/PS1 transgenic mice with hIVIG (Gammagard S/D, Baxter), assessment of anti human IgG antibodies in serum of wild type and transgenic mice, anti human IgG immunostaining in the brain of APP/PS1 mice. **Results:** hIVIG had neuroprotective effect against oligomeric Abeta 1-42 and enhanced the ability of neonatal mouse microglia to degrade human amyloid deposits in ex vivo assay at micromolar concentrations. Immunization of young adult mice with hIVIG at 1g/kg i.p. or i.v. resulted in the formation of neutralizing cross-species antibodies as expected, but tolerance developed after both ways of administration in 4-6 weeks. Intraperitoneal administration of hIVIG once weekly for 14 weeks resulted in significant accumulation of human IgG immunoreactivity in the hippocampus of APP/PS1 mice and in some cases opsonization of amyloid plaques. **Conclusions:** The data suggest that hIVIG contains antibodies that are able to bind Abeta and induce amyloid degradation if provided at high enough concentrations. Development of cross-species immune response and blood-brain barrier do not prevent testing these effects in transgenic amyloid producing mice also in vivo.

47. DECIPHERING CLIOQUINOL ACTIONS ON B6C3TG MICE OVER TIME USING *IN VIVO* MICRODIALYSIS

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Background: In order to study Aβ; thought to be the pathogenic species responsible for AD and a major component of neuropathological plaques; in the ISF of the brains of live animals in real-time, and the effect of drugs targeted towards Aβ, we performed IVM (Cirrito et al., 2003). By inserting probes into live animal's brains, dialysates could be collected and analysed using WB or ELISA. Preliminary studies have shown 1) Cq (1st generation MPAC developed by Prana Biotechnology Ltd targeting metal-amyloid interactions as a therapeutic agent for AD) has an immediate effect on ISF Aβ levels and 2) that the Aβ monomer, as well as higher order species, are detected. The project aimed to examine the underlying mechanism of Cq's effect on Aβ within the brains of transgenic B6C3Tg (double transgenic APPSw/PS1) mice.
Cq treatment causes an initial increase in Aβ levels, but then decreases each day from there on. We wished to reliably reproduce the trend over a number of days and collect sufficient sample for further analysis. **Methods:** Age/sex/transgenic - matched animals were treated with Cq and sacrificed daily in an attempt to elucidate what is mediating Aβ fluctuation, including molecules involved in Aβ degradation or excretion. The mice undergoing IVM were sacrificed and their brains analysed by IHC and WB. **Results & Conclusion:** The study is still ongoing and will combine data for WB and IHC.

48. ARTIFICIAL THETA STIMULATION IMPAIRS CONTEXTUAL FEAR CONDITIONING.

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Background: Several experiments have demonstrated the relationship between hippocampal theta rhythm (4-12Hz) and memory. Lesion of the medial septum or fibria/fornix, a fiber tract connecting hippocampus and the medial septum, results in severe impairment in declarative memory and also abolishes the theta rhythm. **Methods:** Here, using the fear conditioning (FC) paradigm, we investigated whether artificial theta stimulation (ATS) restores fimbria/fornix lesion (FFX) induced memory deficit in rats. Male Wistar rats underwent sham or FFX operation. Stimulation electrodes were implanted in ventral hippocampal commisure and recording electrodes in both septal and temporal hippocampus. Three foot shocks (0.5mA, 100 ms, ISI 64s) were delivered during conditioning. ATS of 8Hz was delivered during FC or during both FC and testing phase 24h later. Memory was assessed by total freezing time upon re-entering the environment 24h after FC. **Results:** ATS impaired fear response in sham and FFX animals. The sham animals that received ATS showed less freezing (40.53±10.03,N=4, mean±S.E.M) than animals which did not receive ATS (69.68±3.77,N=8). Similarly, FFX animals receiving ATS either during FC (37.51±11.41,N=7) or during both FC and test phase (31.12±6.36,N=8) froze less than FFX animals without ATS (57.87±9.06,N=10). **Conclusions:** Disturbing natural theta rhythm by ATS in sham animals reduces fear response. In addition, an attempt to reverse the effect of FFX by ATS leads to greater impairment of fear response.

49. HOOK-PROTEINS IN ALZHEIMER'S DISEASE

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Background: Alzheimer's Disease (AD) is characterised by the presence of two pathohistological hallmarks: beta-amyloid plaques and neurofibrillary tangles. Recent results suggest that AD is associated with aberrant intracellular trafficking and that axonal accumulation of amyloid-precursor-protein (APP) leads to enhanced beta-amyloid generation and deposition.Hook proteins seem to play an important role in intracellular trafficking, aggresome formation and they promote endocytotic trafficking. Since we colocalised Hook1 and Hook3 isoforms with neurofibrillary tangles in human postmorten brain tissue, we wanted to explore the possible role of hook isoforms in Alzheimer's Disease.**Methods:** We investigated the localisation of hook-proteins in different mouse-models of tau expression (human tau, human tau with P301L mutation, tau knock-out and wild-type mice) by immunohistochemistry. Furthermore, we correlated the Braak-stages with the expression of the Hook-isoform mRNAs in adult post-morten brain tissue by RT-PCR as well as with alternative splicing of hook isoforms. In addition we screened embryonic tissue and Hela cells for alternative splicing. **Results and conclusions:** Surprisingly, no alternative splicing products were found in control and AD brain and during development. In contrast to protein quantification, the RT-PCR analysis showed no significant decrease in mRNA levels in AD, hook2-Expression levels even increased. This could be a result of glial activation, since hook2-antibodies stained glial cells in mouse brain tissue. All hook isoforms are expressed in the adult human brain, even though at very different levels.

50. CAREGIVER DEPRESSION IS ASSOCIATED WITH A LOW SENSE OF COHERENCE AND HRQoL

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Background: To examine the SOC of spouse caregivers (n=170). The aim was further investigate the association of SOC, health related quality of life, depressive symptoms, distress and how severity of Alzheimer disease (AD) affects SOC. This study is a part of ongoing intervention study ALSOVA in Finland. The follow-up study includes 241 recently diagnosed AD patience-caregiver pairs which are randomized one of two groups: (a) Intervention group will get intensive psycho educational courses during first two years after diagnosis + traditional care, and (b) traditional care. **Methods:** Caregivers completed Sense of Coherence, 15D, Beck Depression and GHQ scales. The assessment of AD- related symptoms was made using MMSE, CDR, NPI and functional performance using ADCS-ADL scale. **Results:** Male caregivers' sense of coherence was significantly higher than female caregivers. The main predictor for low sense of coherence was depression, with 37% of spousal caregivers reporting depressive symptoms. Women reported more depressive symptoms and distress. Caregivers' HRQoL was high 0.8714. The main predictors for high HRQoL were female gender and low distress. **Conclusions:** Spouse caregivers with low SOC seem to be a vulnerable group of caregivers. The many negative effects of perceived health accumulate in these caregivers during the very early phases of the caregiving process.

NOTES