F1-02-04 PREDICTORS FOR PROGRESSION TO ALZHEIMER'S DISEASE IN MCI SUBJECTS: RESULTS FROM THE GERMAN DEMENTIA COMPETENCE NETWORK (DCN)

Lutz Frolich, *Central Institute for Mental Health, Mannheim, Germany. Contact e-mail: froelich@zi-mannheim.de*

Background: The Dementia Competence Network (DCN) is a comprehensive German multicentre cohort study, which aims for the application of innovative tools in early dementia detection in patients with common preceding symptoms (MCI). Markers of AD investigated in this study include age, other sociodemographic and medical variables, cognitive test performance including MMSE score, the APOE genotype, hippocampus and amygdala volume, and beta amyloid 1-42, total tau, and p-tau 181 levels in CSF. Aim of the presentation is to present data on the best combination of variables for the prediction of AD and to provide data on the predictive accuracy of these variables. **Methods:** Inclusion criteria for this analysis were age >50 years and a new referral to a memory clinic. Exclusion criteria were dementia and disorders causing cognitive impairment. Follow-up assessments were performed annually up to 3 years. Data on the APOE genotype, regional brain volumes, and CSF markers were collected in a subgroup only. Outcome measures were AD and memory impairment at follow-up. Memory impairment was defined as MMSE decline at follow-up. **Results:** MCI Subjects (n = 1080) were at baseline on average 66.9 years old with 9.5 years of schooling, scored 27.1 on the MMSE. 51.4% of the subjects were female. Average follow-up was approximately 2 years. The best set of clinical predictors for AD at follow-up was increased age, and low cognitive performance. Concerning biomarkers, CSF total tau was superior to beta amyloid 1-42 and to volumetric measures of hippocampus and amygdala. The best set of predictors for memory impairment at follow-up were quite similar. Quantitative data for positive and negative predictive values for AD and cognitive decline will be presented. **Conclusions:** Multivariate approaches have a good predictive accuracy for AD at follow-up. Interestingly, among the potential biomarkers, CSF parameters appear to be superior over structural brain volume parameters.

F1-02-05 PREDICTORS OF PROGRESSION IN THE ADNI-MCI COHORT

Paul S. Aisen, *ADCS/UCSD, La Jolla, CA, USA. Contact e-mail: paisen@ucsd.edu*

Background: The Alzheimer's Disease Neuroimaging Initiative (ADNI) is a longitudinal observational study of neuroimaging measures and biochemical biomarkers in amnestic mild cognitive impairment (MCI), mild Alzheimer's disease (AD) and cognitively normal older individuals. One goal is to determine the utility of these measures is predicting decline in the pre-dementia stages of AD. **Methods:** A total of 819 subjects (398 with MCI, and 192 with mild AD, and 229 cognitively normal) were enrolled and have now been followed for over two years. Enrolled subjects were between 55 and 90 years of age and fluent in English or Spanish. MCI subjects had cognitive complaints, an MMSE 24-30, global CDR 0.5 with at least 0.5 in the memory domain, and education-adjusted impairment of approximately 1.5 SD on delayed paragraph recall on the Logical Memory II subscale of the Wechsler Memory Scale−Revised. **Results:** In the MCI cohort, the mean age was 75, 35% were female and 53% carried an APOe4 allele; they had a mean of 16 years of education. At baseline, the mean MMSE was 27.0 ± 1.8, CDR-SB was 1.6 ± 0.9 and ADAScog11 was 11.5 ± 4.4. The annual rate of decline was -0.7 ± 2.5 on the MMSE, 0.6 ± 1.2 on the CDR-SB, and 1.1 ± 4.4 on the ADAScog11. Among the ADNI cognitive and clinical measures, CDR-SB is the most efficient in tracking decline; MRI volumetric measures are more efficient still. Forty percent of the MCI subjects progressed to dementia over 24 months. Baseline cognitive and functional assessments, structural and functional neuroimaging and CSF biomarkers are all associated with conversion to dementia and increased decline on continuous measures. CSF Aß42 below 192 is associated with positive amyloid PET imaging and can be used to select a group with increased progression. Interestingly, CSF Aß42 predicted hippocampal atrophy in individuals with MCI and in the cognitively normal cohort. **Conclusions:** Cognitive, clinical, neuroimaging and CSF biochemical measures are all useful in predicting decline and dementia in subjects with amnestic MCI. Selection of subjects on the basis of low CSF Aß42 may be useful for clinical trials.

F1-02-06 PREDICTORS FOR ALZHEIMER'S DISEASE IN THE NON-DEMENTED SUBJECTS: RESULTS FROM THE DESCRIPA STUDY

Pieter Jelle Visser, *University of Maastricht, Maastricht, Netherlands. Contact e-mail: pj.visser@np.unimaas.nl*

Background: The DESCRIPA study is a European multicentre study, which aims to develop clinical criteria for AD in the predementia stage. Markers of AD investigated in this study include age, the MMSE score, functional impairment, cognitive test performance, the APOE genotype, medial temporal lobe atrophy, and beta amyloid 1-42, total tau, and p-tau 181 levels in CSF. Aim of the presentation is to present data on the best combination of variables for the prediction of AD and to provide data on the predictive accuracy of the recently proposed research criteria for AD (rAD). **Methods:** Inclusion criteria were age >55 years and a new referral to a memory clinic. Exclusion criteria were dementia and disorders causing cognitive impairment. Follow-up assessments were performed annually up to 3 years. Data on the APOE genotype, medial temporal lobe atrophy, and CSF markers were collected in a subgroup only. Outcome measures were AD and memory impairment at follow-up. Memory impairment was defined as AD or amnestic MCI at follow-up. **Results:** Subjects (n = 881) were at baseline on average 71 years old, scored 27.5 on the MMSE, and had 9.5 years of education. 59% of the subjects were female. Average follow-up was 2.1 years. The best set of predictors for AD at follow-up were increased age, low body mass index, and low scores on the MMSE, delayed recall and verbal fluency (area under the curve (AUC) 0.85). The best set of predictors for memory impairment at follow-up were increased age, low score on delayed recall, and decreased ratio of beta amyloid 1-42 and total tau in CSF (AUC = 0.93). The AUC of the rAD criteria for prediction of AD was 0.69 (sensitivity 0.46, specificity 0.91, positive predictive value 0.60) and for memory impairment 0.69 (sensitivity 0.35, specificity 0.95, positive predictive value 0.85). **Conclusions:** Multivariate approaches have a good predictive accuracy for AD at follow-up. Non-demented subjects with memory impairment at follow-up may develop AD at longer follow-up intervals.

SUNDAY, JULY 11, 2010
SYMPOSIUM
S1-01
PREVENTION

S1-01-01 LONG-TERM EFFECTS OF COGNITIVE TRAINING

Sherry Willis, *University of Washington, Seattle, WA, USA. Contact e-mail: oldage@u.washington.edu*

Background: Cognitive training has been shown to improve cognitive abilities in older adults. However, the long term durability of training is seldom assessed, nor the effects on everyday functioning. The ACTIVE trial is the first large-scale randomized trial to examine durability of training gain. **Methods:** A volunteer sample of 2832 persons (mean age 73.6) living independently in 6 US cities was recruited for the ACTIVE trial. Subjects were randomly assigned to one of three interventions (memory, reasoning, speed of processing) or control; training involved 10 sessions. A random sample of those trained received booster training at 11 and 35 months after training. **Results:** Each intervention produced immediate improvement in the cognitive ability trained that was retained across 5 years. Booster training for the reasoning and speed of processing groups produced significantly better performance that remained significant at 5 years.At year 05 participants in all 3 interventions reported less difficulty in performing IADLs compared to control group. This effect was only significant for the reasoning training group. Speed of processing subjects who received booster training performed better than controls on an everyday speed measure at Year 05. **Conclusions:** Compared with the control group, cognitive training resulted in improved cognitive abilities specific to the abilities trained that continued 5 years after

initiation of the intervention. The reasoning training result in less functional decline in self-reported IADLs.

S1-01-02 COGNITIVE IMPAIRMENT OR DEMENTIA IN WOMEN WHO UNDERWENT BILATERAL OOPHORECTOMY BEFORE MENOPAUSE

Walter A. Rocca, *Mayo Clinic, Rochester, MN, USA.*
Contact e-mail: rocca@mayo.edu

Background: In the Mayo Clinic Cohort Study of Oophorectomy and Aging, women who had both their ovaries removed prior to reaching natural menopause experienced a long-term increased risk of cognitive impairment or dementia. In addition, we observed a trend of increasing risk with younger age at the time of oophorectomy. However, women who underwent oophorectomy at young age but were treated with estrogen through age 50 years did not experience an increased risk. **Methods:** Discussion of possible interpretations of the observed association. **Results:** Because the association was observed in a cohort study, we cannot exclude the possibility of confounding. Thus, the association may be non-causal and may have resulted from the confounding effect of genetic variants or of other risk factors. The evidence for a confounding effect is limited. Therefore, we also suggest three possible causal mechanisms for the association: 1) the association may be mediated by an abrupt reduction in levels of circulating estrogen; 2) the association may be mediated by an abrupt reduction in levels of circulating progesterone or testosterone; and 3) the association may be mediated by the increased release of gonadotropins by the pituitary gland in response to the loss of circulating ovarian hormones. These three putative causal mechanisms are probably not mutually exclusive, and may play different roles in different women (heterogeneity of effects at the population level). Thus, we hypothesize that in each woman who undergoes bilateral oophorectomy at young age, the abrupt cessation of ovarian function triggers one or several chains of causality leading to brain lesions in specific regions. The topography of the lesions may vary to some degree across women. It remains unclear whether these lesions are of a degenerative type, a vascular type, or a combination of both. In addition, genetic variants (e.g., in the *APOE* or *ESR1* gene) or non-genetic risk factors (e.g., smoking, obesity) may modify the hormonal effects of bilateral oophorectomy through simple or complex interactions. **Conclusions:** The long-term consequences of bilateral oophorectomy on the brain are an important and understudied area of aging research.

S1-01-03 EXERCISE AND PREVENTION OF DEMENTIA

Carl W. Cotman, *University of California, Irvine, CA, USA.*
Contact e-mail: cwcotman@uci.edu

Background: Behavioral based interventions such as exercise, cognitive training, and diet are emerging as key strategies for preventing age-related cognitive decline and reducing the risk for neurodegenerative diseases. Exercise has been reported in multiple studies to reduce the risk for cognitive decline and conversion to Alzheimer's disease (AD). Moreover, aerobic exercise can improve cognitive function in subjects with mild cognitive impairment and attenuate levels of serum biomarkers linked to age and AD. **Methods:** Human and animal studies. **Results:** In parallel with human studies, studies in rodents and higher animals are defining the mechanisms underlying effects of exercise on brain function. Exercise can improve learning and induce brain derived neurotrophic factor (BDNF), which serves to mediate many of the behavioral effects. Other growth factors and growth factor cascades are also induced by exercise, including IGF-1 and VEGF. Exercise stimulates neurogenesis, vascular growth, and builds synaptic machinery supporting synaptic plasticity, with particularly robust effects in the hippocampus. In addition, long term exercise may increase the capacity for energy production, and reduce inflammation associated with aging and immune challenge. Exercise can even improve learning and reduce brain pathology in transgenic mouse models of AD, including reducing amyloid oligomer levels, indicating that exercise can improve brain function even when pathology is advanced. A key question is how much exercise is needed and how frequently, to attain benefits to brain health and function. Studies in rodents indicate that exercising on alternating days is as effective as daily exercise for induction of BDNF, with BDNF levels remaining elevated for up to 2 weeks after exercise is stopped. Moreover, the benefits to cognition continue to evolve after exercise has ceased, suggesting that the brain continues to encode downstream effects of exercise well after the exercise stimulus has ended **Conclusions:** Taken together, these data suggest that physical activity is a lifestyle intervention that can prevent age-related cognitive decline and can offset brain pathology and cognitive decline associated with AD, even when the disease is at a fairly advanced stage.

S1-01-04 DO STATINS PREVENT DEMENTIA?

Roger Bullock, *Kingshill Research Centre, Swindon, United Kingdom.*
Contact e-mail: roger.bullock@kingshill-research.org

Abstract not available

S1-01-05 DIETARY FACTORS THAT MAY PREVENT DEMENTIA

Martha Clare Morris, *Rush University Medical Center, Chicago, IL, USA.*
Contact e-mail: Martha_C_Morris@rush.edu

Background: Oxidative stress and cholesterol-based metabolic processes are primary biologic mechanisms in Alzheimer's disease and other dementias. **Methods:** The evidence for dietary prevention against dementia is strongest for antioxidant micro-nutrients such as vitamin E and cholesterol-related macronutrients such as a high ratio of polyunsaturated to saturated fat intakes. There is also a convincing literature in support of relations of vitamin B12 and folate to cognitive functioning but the underlying mechanisms and consistency of protection in prospective studies of Alzheimer's disease are not forthcoming. **Results:** What is emerging in the scientific literature is that insufficiencies in most micronutrients as opposed to high intake levels are the important focus for prevention. Vitamin supplementation among persons with adequate vitamin status is not protective for cognitive decline. This is supported by both epidemiologic studies and randomized controlled trials. In one randomized trial, vitamin E supplementation reduced cognitive decline only among persons with dietary intakes lower than the median intake of 6.1 mg/d. Dietary fat composition rather than absolute amounts of fat intake may be the important factor in dementia prevention. A diet that is higher in polyunsaturated or monounsaturated fats and lower in saturated and trans fats appears to be associated with reduced cognitive decline and risk of dementia. A high ratio of n3/n6-polyunsaturated fats also may be associated with lower risk as this fat composition is known to create a vasodilatory, anti-inflammatory state. Fish is a direct source of DHA, the n-3 fatty acid known to be important for brain development. A number of studies have found protective benefit of fish consumption and DHA levels against cognitive decline and incident Alzheimer's disease. The protective benefit appears to be from less than 1 fish meal per week to greater than this amount. The randomized trials of fish oil supplementation have been negative but none of the published or ongoing trials are designed to target non-consumers of fish. **Conclusions:** Insufficient dietary levels of vitamin E and fat composition that results in an unfavorable lipid profile may be associated with increased risk of Alzheimer's disease and cognitive decline. B-vitamin insufficiency or imbalance may be related to poor cognitive decline.

S1-01-06 VASCULAR AND METABOLIC RISK FACTORS FOR DEMENTIA

Deborah Gustafson, *University of Gothenburg and SUNY-Downstate Medical Center, Gothenburg, Sweden. Contact e-mail: deborah.gustafson@neuro.gu.se*

Background: Vascular and metabolic risk factors, such as overweight and obesity, hypertension, high blood levels of cholesterol and homocysteine, and diabetes, increase risk for dementia. Epidemiologic studies have consistently reported on the importance of vascular factors in dementia over the last 20 years and the contribution of vascular events to dementia etiology and progression. However, presence of these vascular risk factors also implies