Dementia (DAD) and Apathy Scale. **Results:** The sample consisted of 52 subjects, 28 with MCI and 24 with dementia (17 mild), aged 82.2 ± 5.0 years, 56% female and with educational level of 2.9 ± 2.4 years. No correlation was found between apathy scores and any global or executive cognitive measure. This finding were observed in the whole sample and where replicated in the MCI, mildly demented and demented sub-samples. Apathy scores inversely correlated with DAD scores in the demented subjects (r = -0.698; p= 0.0011). **Conclusions:** In this community based sample of low-literacy cognitively impaired oldest old elderly, no correlation was found between executive measures and apathy scores. However, higher apathy scores correlated with worse functional performance in the demented patients.

P1-393 HYPERTROPHY OF CA1-HIPPOCAMPAL NEURONS AND APOE FREQUENCY IN ASYMPTOMATIC ALZHEIMER'S DISEASE: FINDINGS FROM THE NUN STUDY

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Background: The pathology of Alzheimer's disease (AD) evolves decades before the disease becomes clinically manifest. Consequently, it is common to find substantial Aβ-plaques (NP) and neurofibrillary tangles (NFT) in the autopsy brains of older subjects with normal cognition, a state we term asymptomatic AD (ASYMAD). Since the CA1 region of the hippocampus is highly vulnerable to AD, here we examine whether CA1 neurons undergo morphometric changes of their cell bodies, nuclei, and nucleoli in ASYMAD subjects. **Methods:** We examined the autopsy brains of subjects with AD pathology and no cognitive deficits (ASYMAD) (n=10) and compared them to age-matched controls (n=13), mild cognitive impairment (MCI) patients with autopsy-confirmed AD pathology (n=5) and AD patients (n=10) from the Nun Study. All subjects underwent neuropsychological evaluations within a year before death. We used the nucleator, a stereological probe, to measure the volumes of neuronal cell bodies, nuclei, and nucleoli in CA1. All subjects were genotyped for APOE. **Results:** We found a significant hypertrophy of the neuronal cell bodies, nuclei, and nucleoli in CA1 of ASYMAD subjects compared to both controls ($p<0.01$) and MCI $p<0.01$). Moreover, a significantly higher allelic APOE2 frequency was present (30%) compared to MCI (0%) and AD (5%) patients in ASYMAD. **Conclusions:** Hypertrophy of CA1 neurons in ASYMAD may represent a reaction to Aβ or tau, long before the onset of cognitive decline, or may constitute a surrogate for the activation of cellular processes that forestall the progression of AD and the development of dementia. Future understanding of the changes in gene or protein expression underlying the neuronal hypertrophy in ASYMAD may provide clues to the pathogenesis and eventual therapy of AD. For example, we are planning to study in ASYMAD the expression of Rheb (ras homolog enriched in brain), a gene important for neuronal growth. The high frequency of APOE2 alleles among ASYMAD subjects is puzzling. Since these subjects do have Aβ deposits, the APOE2 allele may provide protection from AD not only by preventing Aβ deposition, but also by promoting growth and repair of injured neurons and neurites.

P1-394 VARIATION IN PLACEBO DECLINE ACROSS A DECADE OF ALZHEIMER'S DISEASE TRIALS

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Background: It has been suggested that placebo-treated patients are showing slower rates of cognitive decline in recent Alzheimer's disease (AD) clinical trials compared with older trials. Systematic changes in placebo decline might impact treatment effects and AD treatment trial results. The objective of these analyses was to use an extensive database of donepezil studies to investigate: (1) variations in rates of placebo decline in AD studies conducted between 1991 and 1999, and (2) any subsequent impact on donepezil treatment effect. **Methods:** A meta-analysis was conducted using individual patient data from relevant randomized, double-blind, placebo-controlled studies of donepezil for AD. Data were grouped according to the year of initiation of the trials. Group 1 (pre-1995): studies initiated in 1990-1994; Group 2 (post-1995): studies initiated in 1996-1999. This cut-off is associated with the timing of donepezil registration. Changes from baseline Mini-Mental State Examination (MMSE) and Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) scores up to Week 24 were compared between groups 1 and 2 for placebo only; and then between donepezil and placebo. Analyses used the last observation carried forward method. **Results:** Data were available from 3748 patients who participated in 14 randomized, double-blind, placebo-controlled AD trials. Group 2 (post-1995) patients had lower baseline MMSE scores, were older, had fewer males in the population, had more comorbidity and used more concomitant medications. Least squares mean decline on the MMSE from baseline to Week 24 was significantly greater among placebo patients in group 1 (-1.26 points) compared with group 2 (-0.54 points; $P = 0.026$); placebo decline on the ADAS-cog was also greater in group 1 (+1.81 points) than group 2 (+1.02 points), but the difference was nonsignificant ($P = 0.14$). Of note, a comparable donepezil-placebo treatment difference was observed in groups 1 and 2, indicating that the treatment effect was consistent over the decade of enrolment. **Conclusions:** The results indicate that patients with AD entering clinical trials are experiencing slower rates of cognitive decline. This finding has implications for future clinical trial design and treatment planning.

P1-395 Fe, Zn, Se AND Na INCREASES IN BRAINS OF INDIVIDUALS WITH COGNITIVE DECLINE

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Background: Although it has been known that trace elements play an essential role in the human metabolism, the role of these elements in neurological diseases still remains uncertain. **Methods:** Brain samples from 22 normal and 28 demented individuals of both genders aged more than 50 years from the Brain Bank of the Brazilian Ageing Brain Study Group. The brain samples were cut using a titanium knife and then freeze-dried. Neutron activation analysis was applied to assess Fe, Zn, Se, Na, K, Rb concentrations. Certified reference materials, NIST 1566b Oyster Tissue and NIST 1577b Bovine Liver were analyzed for quality of the analytical results. Cognitive evaluation was retrospectively gathered through a semi-structured interview using the Clinical Dementia Scale (CDR) and Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE). Participants were classified as cognitively normal if the CDR was 0 and the IQCODE <3.20 and as demented if the CDR was ≥ 2 and the IQCODE 3.80. **Results:** Comparisons between the results obtained for the hippocampus of normal and demented individuals showed significantly higher concentrations of Fe, Na, Se and Zn in the hippocampus of demented individual group (p=0.05). On the other hand, the hippocampus of the demented group presented lower K and Rb concentrations when compared to the hippocampus of the normal group. **Conclusions:** It is possible that the disequilibrium found in this study could be related to cognitive decline. However, further analysis with a larger group of both normal and demented individuals, including intermediate rates of cognitive decline, is needed.