β-amyloid (Aβ)-rich regions of the brain is a distinct feature of Alzheimer's disease (AD). Compelling evidence shows a strong correlation between accumulation of aggregated neurotoxic b-amyloid peptides and oxidative stress in the brains of patients afflicted with AD. One hypothesis for this correlation involves the direct and harmful interaction of aggregated Aβ peptides with cellular proteins responsible for maintaining normal, cellular levels of reactive oxygen species (ROS). **Objective:** To identify specific, destructive interactions of Ab peptides with cellular antioxidant enzymes and to inhibit these harmful protein-amyloid interactions. **Methods:** Using cell-free and cellular assays, in addition to fluorescence microscopy, we demonstrate that exposure of human neuroblastoma cells to cytotoxic preparations of aggregated Ab peptides results in significant intracellular co-localization of Ab with catalase-an antioxidant enzyme responsible for catalyzing the degradation of the ROS, hydrogen peroxide (H_2O_2)-and that these catalase-Ab interactions contribute to an observed increase in cellular levels of H_2O_2. Furthermore, we evaluate the effects of generating protein-resistive surface coatings on aggregated Ab peptides in cells by using two oligo(ethylene glycol) derivatives of 6-methylbenzothiazole aniline (BTA-EG_4 and BTA-EG_6) as synthetic molecular probes that exhibit the following characteristics: 1)capability of generating protein-resistive surface coatings on aggregated Ab peptides (to inhibit catalase-amyloid interactions in cells), 2)lack of toxicity, 3)cell permeability, 4)capability of localizing to the same subcellular compartments of cells as Ab, 5)intrinsic fluorescence properties (to visualize the intracellular localization of the molecules), and 6)chemical stability in oxidative environments. We show that these small molecule inhibitors of catalase-amyloid interactions protects the hydrogen peroxide-degrading activity of catalase in an Ab-rich environment, leading to reduction of the co-localization of catalase and Ab in cells, inhibition of Ab-induced increase in cellular levels of H_2O_2 (Figure 1), and neutralization of the toxicity of Ab peptides. **Conclusion:** These studies provide evidence for the important role of catalase-amyloid interactions in Ab-induced oxidative stress and propose a novel molecular strategy to inhibit such harmful interactions in AD.

P4-315 SEVERE PSYCHOLOGICAL STRESS IN THE ELDERLY: A PROPOSED MODEL OF NEURODEGENERATION

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Background: Although there were implications on the way stress events affect memory and cognition, not many studies have been performed. The majority of these studies measured hippocampal volume in patients with PTSD (Post Traumatic Stress Disorder). Hippocampus which plays a vital role in memory formation was found to be of reduced volume in people who suffered PTSD compared to control subjects Many similarities are observed between PTSD and Alzheimer's Disease, such as (a) Hippocampus is the most vulnerable brain structure (b) The first symptom is memory problems, (c) Increased levels of glucocorticoids (GCs) are observed in both conditions and (d) there is the same prevalence of women/men ratio 2:1 in both diseases. **Objective:** The objective of our study is to examine the possible effect of severe psychological stress on cognitive function. **Methods:** In a recent study our results showed that the majority of patients reported a past stressful event just before the onset of dementia (n = 990, 77.9%), whereas less patients reported insidious onset (n = 281, 22.1%). The prominent stressful event was the announcement of a life-threatening disease (n = 472, 37.1%), followed by problems within the family (n = 157, 12.4%), spouse death (n = 100, 7.9%), and death of a sibling or other beloved person (n = 77, 6.1%). **Conclusion:** This study supports the idea that some elderly people have increased tendency to develop dementia after a stressful event than others. This might be due to a genetic predisposition of a certain elderly population, who carries specific genes, an hypothesis which needs further and thorough investigation. Recent study showed that a deletion variant of ADRA2B, the gene encoding the *a*2b-adrenergic receptor, is related to enhanced emotional memory. The evidence collected to date is consistent that initial cognitive symptoms of a Severe Psychological Stress event may: (a) increase vulnerability to stress, (b) make neurons more sensitive to the GCs as we age, and (c) alter the regulation of the GC receptors. It is well known that plasticity of brain is changed in the elderly and perhaps acute stress is another pathogenic mechanism of neurodegeneration.

P4-316 PHARMACOLOGICAL VALIDATION OF THE CANINE MODEL OF ALZHEIMER'S DISEASE: DONEPEZIL IMPROVES MEMORY IN COGNITIVELY IMPAIRED AGED BEAGLE DOGS

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Background: Aged Beagle dogs provide a unique model of Alzheimer's disease because they can show both cognitive impairment and pathological changes. **Objective:** This study examined the effects of the cholinesterase inhibitor donepezil at two dose levels (1.5 and 6mg/kg/d PO) on memory in aged Beagle dogs assessed by performance on a delayed non-matching to position task (DNMP). **Methods:** On each trial, the dogs were first presented with an object in one of three locations. After a delay of either 20 or 90 s, the dog was then presented with two identical objects; one at the sample location, and the other in one of the remaining two locations, which was the correct response. Initially, 34 dogs were given five baseline sessions on the DNMP, were randomized to similar groups, and were then washed in at a fixed dose over 5 days. During the assessment, each subject was tested at 1, 3 or 5hours following dosing with three tests at each post-dose delay. **Conclusion:** The analysis revealed that the high dose impaired memory when compared to both the low dose and placebo groups particularly at 3 and 5 hours. The analysis also revealed improved performance in the low dose donepezil group at 5 hours compared to both placebo and baseline performance, but only in low and moderate performing animals. Plasma concentrations of donepezil in the low dose were similar to efficacious levels in humans (i.e. 25 - 50 ng/ml). In the high dose group, levels were several times higher and cholinergic side effects were evident. The current study indicates that memory improvement by donepezil is highly linked to plasma concentrations and may be most robust in cognitively impaired populations, both of which have been suggested in other species. On the other hand, the short treatment schedule may have prevented us from seeing longer term cognitive benefits at the doses tested. The current study indicates the canine model demonstrates pharmacological validity in predicting true positives in addition to our previous findings of predicting false positives. Collectively, our findings support the use of the dog for screening Alzheimer's disease therapeutics.

P4-317 ALZHEIMER'S PATIENTS EXHIBIT DEFECTIVE SERUM CERULOPLASMIN ASSOCIATED WITH DEFECTIVE COPPER BINDING

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Background: Copper dyshomeostasis and chronic copper exposure have been implicated in the progression of AD. (Sparks, L. et al, 2003, Squitti, R. et al, 2009, Morris MC 2007). Wilson's Disease (WD) a treatable liver disease of copper dyshomeostasis having neurologic manifestations has defective serum copper transport protein ceruloplasmin and elevated ''free'' non-ceruloplasmin-bound serum copper. Chronic copper exposure is contraindicated in WD and patients are treated with oral zinc. No reliable serum based marker exists for AD. **Objective:** A prospective, blinded, clinical study mounted at the Alzheimer's Center, Albany Medical Center, provided sera for the comparison of both free and bound copper in AD patients and age-matched normals, and the concentration and composition

of ceruloplasmin. **Methods:** After IRB approval, normal subjects were recruited by referral and media. AD patients not taking zinc or copper supplements were recruited from the Center's clinical practice by standard tests and NINDS-ADRDA criteria. AD patients (n = 29, avg age 79) and normals (n = 29; avg age 69) provided morning draw blood after overnight fast, immediately spun to serum andfrozen at -80°. Samples were analyzed after a single thaw, in a blinded manner. Ceruloplasmin was measured immunoturbimetrically (Roche analyzer) and also by enzymatic activity assay (Schmidt Schott method); total serum copper by atomic absorption. **Conclusion: Results:** AD and normal patients had comparable serum ceruloplasmin levels. AD patients had significantly lower ceruloplasmin oxidase activity ($p = 0.004$). The serum copper to ceruloplasmin ratio was substantially lower in AD ($p = 0.00008$) indicating less copper bound per unit of immunologically measured ceruloplasmin in AD. Percent serum copper not bound to ceruloplasmin (with ceruloplasmin measured enzymatically) was 31% higher in AD compared to normals ($p < 0.045$).Conclusion: These data find a significant percentage of defective serum ceruloplasmin determined by oxidase activity in AD patients and that such defect is associated with ceruloplasmin lacking bound copper. As in Wilson's disease, defective ceruloplasmin in AD may imply reduced capacity to protect from chronic copper exposure. A serum based assay based on these findings and parameters may be of clinical benefit. The nature and origins of the defective ceruloplasmin in AD particularly warrant further study.

P4-318 DIFFERENTIATING ALZHEIMER'S DISEASE FROM VASCULAR DEMENTIA WITH EEG FUNCTIONAL NEUROIMAGING

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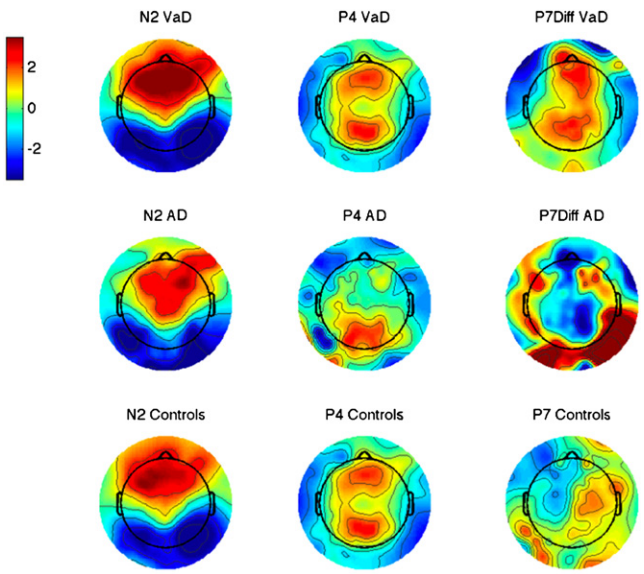
Background: Differential diagnosis of Alzheimer's disease (AD) and vascular dementia (VaD) is challenging because early symptoms are similar despite different underlying neuropathology. In previous research, we found that a computerized associative memory task coupled with high resolution EEG measures differentiated mild AD from healthy controls (85% sensitivity, 93% specificity). We extend this functional imaging technique to identify differential diagnostic markers in AD and VaD. **Objective:** Participants included untreated patients newly diagnosed with probable AD (N = 8), VaD (N = 8), and controls (N = 8). Patients were matched for MMSE scores, and all participants were matched for age and gender. Each participant completed a 20minute computerized memory task. Stimuli consisted of simple visual images paired with associatively related auditory words. Participants were required to respond Old or New by button press on each trial. EEG (128 channel) was recorded continuously during the task. We examined ERP components including the N100, P100, N200, P300, P400, P600, a difference wave at 700 ms, and behavioral responses (d'). Each variable was assessed individually using binary logistic regression, and sensitivity and specificity profiles were constructed. Next, the best classifiers were entered into regression analyses in pairs, and then in groups of three. **Methods:** Good discrimination was achieved by several combinations of 2 and 3 variables, with sensitivity ranging from 62% to 87.5%, and specificity from 75% to 87.5%. The best classification between AD and VaD groups was achieved by a centro-parietal N200 amplitude difference combined with the 700ms difference wave (87.5% sensitivity and 87.5% specificity). These same ERP variables also discriminated between VaD patients and controls (75% sensitivity and 75% specificity). The behavioral measure (d' statistic) discriminated between controls and the two patient groups, but not between AD and VaD groups. **Conclusion:** Despite similarity in early symptoms in AD and VaD, differences in the underlying neuropathology may produce a reliably different signature in the EEG signal. We found that specific combinations of ERP effects generated during a controlled memory test provide good sensitivity/specificity with respect to AD, VaD, and matched controls. Such functional biomarkers may offer a clinically useful aid in differential diagnosis of common forms of dementia.



Topographic averaged ERP plots: columns show N200, P400, and P700 effects, rows show vascular dementia patients, Alzheimer's disease patients, and controls (outer circle represents signal from lateral planes).

P4-319 PERLECAN DOMAIN V INHIBITS BRAIN ENDOTHELIAL CELL ABETA TOXICITY IN VITRO

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Background: Recent evidence suggests a critical vascular component to Alzheimer's disease pathology. Among other discoveries, amyloid-beta (Abeta) has demonstrated toxicity to cerebral microvascular endothelial cells. The exact mechanism(s) of such endothelial cell toxicity remain to be elucidated. **Objective:** We hypothesized that Abeta might kill endothelial cells via direct interactions with the endothelial cell alpha5beta1 integrin, an important extracellular matrix receptor expressed on activated/angiogenic endothelium. Furthermore, in an effort to identify potential endogenous inhibitors of Abeta endothelial cell toxicity, we investigated whether the C-terminal domain V (DV) protein fragment of the vascular basement membrane proteoglycan component, perlecan, a potential competitive ligand of alpha5-beta1 integrin, could inhibit Abeta endothelial cell toxicity. **Methods:** In both cases, toxicity was measured with MTS solution after 24hours of exposure to 10 micromolar Abeta25-35 in vitro. **Conclusion:** We could significantly inhibit Abeta25-35 endothelial cell toxicity with alpha5beta1 function blocking antibody (10 micrograms/ml) and with DV (300 nM) ($P < 0.0001$ for both). Furthermore, as DV is proteolytically processed from perlecan's protein core during times of vascular remodeling and injury, we propose that it could represent a natural brain defense against Abeta endothelial cell toxicity that could be exploited therapeutically to improve vascular pathology in Alzheimer's disease.

P4-320 EVIDENCE OF AN INTERACTION BETWEEN APOE AND IDE IN KETONE BODY THERAPIES IN MILD TO MODERATE ALZHEIMER'S DISEASE

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Background: Alzheimer's disease (AD) is characterized by early and region-specific declines in cerebral glucose metabolism. A 90-day, double-blind, placebo-controlled trial of the the ketogenic compound AC-1202, was conducted in patients with mild to moderate Alzheimer's disease. Patients administered AC-1202 who lacked the epsilon 4 variant of the APOE gene (E4(-)) demonstrated significant differences in change from Baseline in the Alzheimer's Disease Assessment Scale-Cognitive (ADAS-