

POSTER PRESENTATION ABSTRACTS

BASIC

Poster 1

MEDROXYPROGESTERONE ACETATE, THE MOST COMMONLY USED HORMONE THERAPY PROGESTIN, IMPAIRS MEMORY AND ALTERS THE GABAERGIC SYSTEM IN THE RODENT MODEL. Braden BB, Talboom J, Simard A, Lukas RJ, Zay C, Prokai L, Acosta J, Engler E, Bimonte-Nelson HA. Arizona State University; Barrow Neurological Institute; University of North Texas; Arizona Alzheimer's Consortium.

Background: Women with a uterus must add a progestin to their hormone therapy to offset the estrogen-induced increase in endometrial cancer. There is evidence that in menopausal women Prempro (estrogens + the synthetic progestin medroxyprogesterone acetate; MPA) has a greater negative impact on cognition than estrogens alone. We have shown that tonic treatment with natural progesterone impairs memory (Bimonte-Nelson et al., 2004) and reverses the cognitive-enhancing effects (Bimonte-Nelson et al., 2006) and neurotrophin increases (Bimonte-Nelson et al., 2004) due to 17 β -estradiol treatment in older ovariectomized (Ovx) rats. In the current study, we extend these findings by evaluating the mnemonic effects of MPA. Also, several metabolites of progesterone have a high affinity for the GABA_A receptor (Paul & Purdy, 1992), and progesterone administration decreases glutamic acid decarboxylase (GAD) (i.e. the synthesizing enzyme and rate limiting step of GABA production) activity in the dorsal hippocampus of the rat (Wallis & Luttge, 1980). Importantly, the hippocampus and other brain regions that play a crucial role in memory processing are largely controlled by the GABAergic system (Izquierdo et al., 1993). This led to our hypothesis that progesterone- and MPA- induced memory impairments may be, in part, due to GABAergic modulation.

Methods: Aged Ovx rats were given tonic subcutaneous vehicle (propylene glycol), progesterone, or one of two doses of MPA. Rats were tested for spatial working and reference memory on the water radial-arm maze (RAM), and then for spatial reference memory on the Morris maze (MM). Additionally, we evaluated cognitive brain regions for changes in the GABAergic system in the animals that were behaviorally tested.

Results: On RAM, aged Ovx rats given progesterone (OVX+PROG) and high MPA (OVX+High MPA) made more working memory errors at the highest memory load as compared to Ovx controls. OVX+High MPA animals continued to make more working memory errors after a 2 hour delay. The OVX+High MPA group also showed greater overnight forgetting on the MM, as compared to Ovx controls. Western Blot analyses showed that both progesterone and MPA decreased GAD protein levels in the hippocampus and increased GAD protein levels in the entorhinal cortex.

Conclusions: These data suggest that progesterone and MPA can be detrimental to working and reference memory, as well as modulate the GABAergic system in cognitive brain regions, in an aged animal model of surgical menopause. Further research better defining the parameters of how this widely used synthetic progestin, MPA, detrimentally influences the brain and cognition is warranted, including more detailed preclinical basic science studies and clinical evaluations in women.

Poster 2

ANDROSTENEDIONE IMPAIRS SPATIAL REFERENCE AND WORKING MEMORY IN MIDDLE-AGED SURGICALLY MENOPAUSAL RATS. Camp BW, Villa S, Gerson, J, Bimonte-Nelson, HA. Arizona State University; Arizona Alzheimer's Consortium.

Objective: After natural menopause, androstenedione becomes the primary hormone secreted by the residual follicle deplete ovaries. Recent research from our laboratory (Acosta et al. 2009a) has shown a correlation between higher androstenedione blood serum levels and working memory errors in middle-aged rats with menopausal follicular deplete ovaries. The current study is the first to directly examine the cognitive effects of androstenedione in a rodent model.

Methods: Middle-aged ovariectomized rats received vehicle or one of two doses of androstenedione (4 or 8 mg/kg daily). Rats were tested on a spatial working and reference memory maze battery including the water radial arm maze (WRAM), Morris water maze (MM), and delay match to sample task (DMS).

Results: We found that androstenedione at the highest dose impaired reference memory as well as the ability to maintain performance as memory demand was elevated. This was true for both high demand memory retention of one item of spatial information as well as the ability to handle multiple items of spatial working memory information.

Conclusions: These findings suggest that androstenedione, the main hormone produced by the follicle deplete ovary, is detrimental to spatial learning, reference memory, and working memory.

Poster 3

ORAL PREMARIN TREATMENT DOSE- AND TASK- DEPENDENTLY INFLUENCES MEMORY IN MIDDLE-AGED SURGICALLY MENOPAUSAL RATS. Engler-Chiurazzi E, Scheldrup M, Ciciolla L, Braden BB, Acosta J, Talboom J, Demers L, Prokai L, Baxter L, Bimonte-Nelson HA. Arizona State University; Pennsylvania State College of Medicine; University of North Texas; Barrow Neurological Institute; Arizona Alzheimer's Consortium.

Background: Premarin is an equine-derived complex estrogen formulation used as hormone therapy in menopausal women. Orally-administered Premarin is the most commonly prescribed estrogen therapy, and was the estrogen therapy used in the Women's Health Initiative study. Although in vitro studies suggest that Premarin is neuroprotective, and we have shown that subcutaneously administered Premarin enhances memory in the rat (Acosta et al., 2009; Engler-Chiurazzi et al., in press), no study has tested the effects of Premarin on cognition in an animal model using an oral route of administration. Characterizing the effects of oral Premarin is important given that 1) estrogen metabolism varies depending on route of administration, and 2) oral administration is the primary route by which women take Premarin (Hersh et al., 2004).

Methods: The current experiment tested whether oral Premarin treatment impacted spatial and nonspatial learning and memory, using a maze battery, in the middle-aged ovariectomized (Ovx) rat. Rats received oral administration (hand fed via a syringe filled with condensed milk and distilled water) of Vehicle, Premarin-Low, Premarin-Medium or Premarin-High treatment. The low dose was comparable to the 0.625 mg daily dose women take, adapted for body weight of the rat.

Results: The Premarin-High treatment increased working memory errors during acquisition of a spatial delayed-match-to-sample task. There was also an impairment reflecting a dose-response pattern after a 6-hour delay on this task. However, on the non-spatial black/white discrimination task, Premarin-Medium treatment resulted in faster task acquisition. Measurement of nerve growth factor (NGF) protein levels revealed that Premarin-High treatment decreased NGF protein levels in the frontal cortex, while increasing NGF levels in the posterior cingulate cortex. All Premarin doses resulted in positive vaginal smears and a dose-response increase in serum levels of estrone and estradiol, uterine weights and pituitary weights.

Conclusions: These findings suggest that oral Premarin provides divergent effects on memory depending on the dose and the type of memory assessed, and that growth factors are affected in a dose dependent manner by oral Premarin treatment as well. Of note, the detrimental effects of oral Premarin treatment on spatial working memory are in contrast to our previous findings showing that subcutaneous Premarin treatment enhanced spatial working memory. Further evaluations directly comparing routes of administration, and the assessment of potential mechanisms through which the route of administration can produce differences in Premarin effects on the brain will help optimize treatment benefits from this hormonal preparation.

Poster 4

CONCEPT FOR A BRAIN TISSUE SCREENING PROCEDURE TO ENSURE PRION EXCLUSION. Hartmann EM, Halden RU. Arizona State University; Arizona Alzheimer's Consortium.

Background: In 1996, a novel, contagious form of dementia was discovered, dubbed variant Creutzfeldt-Jakob disease (vCJD). This disease is caused by the consumption of meat from cattle affected with bovine spongiform encephalopathy, although it is symptomatically and pathologically similar to the most common form of dementia, Alzheimer's disease. Undetected cases of vCJD pose a significant risk to brain banks storing large quantities of brain tissue from demented individuals and to researchers working with said tissues. The most imminent risk is pathogen exposure of the people directly handling the tissues. Additionally, these tissues may come from misdiagnosed patients, confounding results from studies of dementias having other etiologies. A sensitive, high throughput method for the detection of the causative agent of vCJD would aid in mitigating these risks.

Methods: A previously introduced nanospray liquid chromatography/tandem mass spectrometry method is proposed for adaptation to enable the detection of pathogenic prion protein in human samples. An additional biomarker for the detection of all prion proteins is proposed to supplement the original method. A potential experimental setup to demonstrate the efficacy of this method is also described. This setup could also be used to investigate the incidence of vCJD misdiagnosis or comorbidity with other dementias, such as Alzheimer's disease.

Conclusions: Insufficient exclusion of pathogenic prion infected tissues could have detrimental effects on the people and institutions that collect affected tissues, including donor organs and blood. Screening for the pathogenic agent in these tissues would prevent further damage. Effective screening is an attainable goal using the methods outlined here.

Poster 5

ISOLATING SCFV AGAINST NATURAL BETA AMYLOID OLIGOMERS – A NOVEL THERAPEUTIC STRATEGY FOR ALZHEIMER’S DISEASE. Kasturirangan S, Boddapati S, Reasoner T, Sierks M. Arizona State University; Arizona Alzheimer’s Consortium.

Soluble cell-derived oligomers of A β have been shown to play a critical role in disrupting synaptic plasticity and behavior. We have previously described a bio-panning technique to isolate scFvs against different morphologies of A β . The panning was done on a mica substrate against synthetically derived oligomers, and requires a constant and high (micro-molar) concentration of oligomers for both the panning and particularly the screening processes. Here we describe a modified bio-panning protocol which can be used to identify scFvs against low (nano-picomolar) quantities of cell-derived A β dimers. The method involves performing negative panning first against the cell derived control samples followed by stringent negative panning against synthetic monomers. Removal of all phage that bind to non-desired control antigens can be verified by atomic force microscopy (AFM). Once all phage binding to control antigens other than A β dimers are removed, the recovered phage are then added to the oligomer sample. Any bound phage to the dimer sample should represent phage expressing scFvs that bind the cell derived oligomeric A β aggregates, but not monomeric A β or other cell derived proteins. Further rounds of panning and enrichment by increasing the concentration of the monomers in the negative panning steps and lowering the concentration of soluble oligomers enabled isolation of scFv candidates with highest affinity toward oligomeric A β . Combining the imaging and nano-manipulation capabilities of AFM with the protein diversity of the phage library, we can recover any single phage molecule bound to a target oligomeric A β molecule.

Poster 6

A MULTIMODAL BIOCHIP TO STUDY CONTROLLED GENE DELIVERY TO NEURONS.

Sridharan A, Patel C, Muthuswamy J. Arizona State University; Arizona Alzheimer's Consortium.

Background: RNAi based therapeutics represent a promising strategy to alleviate symptoms for neurodegenerative disorders such as Alzheimer's disease. Although siRNA molecules offer targeted suppression of key genes in a selected pathway, significant impediments to overcome are 1) the efficient and controlled delivery of multiple siRNAs to neurons, 2) the potential lethality of total gene suppression, and 3) effective maintenance of neuron functionality. To address these issues, we have developed a multimodal platform that is capable of targeted delivery and electrophysiological monitoring using a microelectrode array (MEA).

Methods: In this paper, we compare current, chemical based gene delivery methods to a multimodal MEA platform that is capable of microscale electroporation and neural recordings *in vitro*. We transfected various rodent based cell-lines (3T3 fibroblasts, Neuro2A neuroblastoma, and primary neurons with multiple vectors, including GFP plasmids, scrambled siRNA sequences, and gene-specific siRNA. We compared the transfection efficiencies of conventional chemical transfection agents, such as Lipofectamine™ and SilentFect™, and with MEA based microscale electroporation.

Results: MEA based electroporation is demonstrated for various cell-lines, from 3T3 to primary neurons from rats. Transfection with siRNA of 3T3 cells yielded 60% transfection efficiency with >80% viability. A 4V, 1 ms pulse of primary neurons yielded similar results to 3T3 cells with a 56% efficiency and 82% viability. Second generation transparent ITO-MEA devices showed similar efficiencies for 3T3 (75% efficiency). Successful neuronal recordings were obtained after 7DIV. In comparison, transfection using chemical agents was highly variable. Chemical transfection efficiencies for easy-to-transfect cell lines, such as Neuro2A and 3T3, ranged from 45-90% for siRNA, depending on the chemical agent, concentration, and binding/association kinetics. 50-70% transfection efficiencies were achieved for larger gene delivery vectors (GFP plasmid, 5.8 kB). Simultaneous co-transfection with GFP plasmid and siRNA sequences suggested a varied cell expression response that depended on transfection agent and siRNA dose. Lipofectamine™, for example, preferentially transfected GFP plasmid vectors compared to GFP siRNA, whereas SilentFect™ showed a dose-dependent siRNA based suppression of GFP expression. Transfection of neurons using chemical agents yielded 3-5% transfection efficiencies for GFP plasmids and 50-80% for individual siRNA sequences. However, co-transfection studies with siRNA and GFP plasmids with primary neurons yielded inhomogeneous and skewed transfection into cells.

Conclusions: This paper demonstrates that microscale electroporation using a multimodal MEA biochip yielded consistent transfection efficiencies and high viabilities for neurons with spatio-temporal control. Transfection efficiencies seem to be independent of cell lines. In comparison, chemical transfection agents were unable to deliver consistent transfection efficiencies across cell lines. In addition, inhomogeneous transfection was observed for multiple gene vectors. A multimodal MEA biochip that is capable of consistent delivery of gene constructs and subsequent assessment of its electrophysiological effect on neurons on the same platform will be useful in studying novel multi-pronged therapeutic strategies for Alzheimer's disease.

Poster 7

$\Delta^{8,9}$ -DEHYDROESTRONE, A COMPONENT OF PREMARIN, ENHANCES SPATIAL MEMORY AND ALTERS CHOLINERGIC NICOTINIC RECEPTOR EXPRESSION.
Talboom JS, Engler-Chiurazzi EB, Whiteaker P, Simard AR, Lukas R, Acosta JI, Cosand M, Prokai L, Bimonte-Nelson HA. Arizona State University; Barrow Neurological Institute; University of North Texas; Arizona Alzheimer's Consortium.

Background: Ovarian hormone loss at menopause has been related to cognitive decline, and some studies suggest that hormone therapy (HT) can mitigate these effects. Recently, the Women's Health Initiative Memory study found that Premarin, the most commonly prescribed HT composed of conjugated equine estrogens, had null or detrimental cognitive effects. These findings suggest that neither ovarian hormone absence nor the most commonly prescribed HT are optimal for cognition. Isolated Premarin components have been evaluated in vitro (Brinton et al., 1997; Zhao and Brinton, 2006), with $\Delta^{8,9}$ -dehydroestrone (Δ^8E1) and equilin showing the strongest neuroprotective profile, suggesting that select isolated components are more efficacious than others. These Premarin components have not been evaluated for effects on cognition or cholinergic function, a system that modulates cognition.

Methods: We evaluated Δ^8E1 and equilin treatments in middle-aged ovariectomized rats, on a cognitive battery, nicotinic acetylcholine receptor (nAChR) expression using radioligand binding analysis, and function of heterologously expressed, human $\alpha4\beta2$ -nAChRs after acute or prolonged exposure to the Premarin components.

Results: Δ^8E1 enhanced spatial working and reference memory and decreased numbers of hippocampal and entorhinal cortical ^{125}I -labeled epibatidine binding sites, predominantly reflecting $\alpha4\beta2$ -nAChR expression. In Δ^8E1 treated animals, less hippocampal nAChR binding was correlated with better spatial reference memory performance. Equilin did not affect cognition and had minimal effects on nAChR-specific radioligand binding levels. Neither estrogen directly affected human $\alpha4\beta2$ nAChR function. Both estrogens influenced vaginal smears, uterine weights, and serum luteinizing hormone levels, analogous to classic estrogens.

Conclusions: These findings indicate that specific isolated Premarin components differ in their ability to affect cognition and nAChR expression, and they identify Δ^8E1 as a novel hormone that could broaden the scope of investigations towards optimizing HTs that benefit brain health and function during aging.

Poster 8

POLYNUTRIENT DIETARY SUPPLEMENTATION CORRECTS BRAIN MITOCHONDRIAL BIOMARKERS AND IMPROVES COGNITION IN THE 3XTG MOUSE MODEL OF ALZHEIMER'S DISEASE. Wolf AB, Braden BB, Hatch M, Young N, Enger E, Garcia A, Bowman B, Kusne Y, Lombardo NE, Bimonte-Nelson H, Valla J. Barrow Neurological Institute; St. Joseph's Hospital and Medical Center; Arizona State University; Boston University School of Medicine; Veterans Administration Medical Center; Arizona Alzheimer's Consortium.

Background: Animal model and epidemiological studies suggest that some diets can be neuroprotective and slow cognitive decline in early stage AD. An interdisciplinary team of clinicians and nutritionists designed the Memory Preservation Nutrition Supplement Program (MPNSP), designed to deliver diverse, broad-based, high-quality nutritional supplementation for aging populations.

Methods: We administered MPNSP supplements incorporated into standard mouse chow to triply-transgenic mice known to develop features of AD with age, including significant, progressive, and brain region-specific changes in mitochondrial function. Mice (N=56) were fed either supplemented or standard chow beginning at an average age of 38 weeks (range 29-46 weeks) in age- and sex-matched cohorts in a full 2x2 design (genotype x diet). After 4 months of supplementation, mice were cognitively tested on a delayed match to position (DMP) spatial working and recent memory plus maze task, followed by an evaluation of memory retention by testing DMP performance after a 30 minute delay, as well as the spatial reference memory Morris maze. Subsequently, their brains were processed for mitochondrial cytochrome oxidase histochemistry and neuroanatomic densitometric imaging.

Results: Behaviorally, the supplemented diet enhanced learning of the DMP task in male 3xTG mice. The female 3xTG mice not receiving the enhanced diet were the only group impaired by a 30-min delay on the DMP task, indicating diet-induced protection for this increased memory demand in females. Male 3xTG mice, with or without the supplemented diet, were not impaired on this measure. There were no diet effects on the Morris maze. Supplementation also significantly corrected 3xTG mitochondrial function, in a brain region-specific, and often sex-specific, fashion. Studies are underway to deduce the effects of the supplementation on additional markers of AD in these mice.

Conclusions: Collectively, these findings, taken with prior research, indicate that diet could be a safe and cost-effective method of influencing AD-related functional change.

Poster 9

AGE-RELATED COGNITIVE IMPAIRMENT IN APOE TRANSGENIC MICE. Yin J, Lin H, Marsh ST, Shi J. Barrow Neurological Institute; St. Joseph's Hospital and Medical Center; Dongzhimeng Hospital Beijing University of Chinese Medicine; Arizona Alzheimer's Consortium.

Background. It has been reported that human apolipoprotein E (hApoE) is critical for neuronal maintenance and repair. There are three common isoforms of ApoE, E2, E3 and E4. Compared with E3, E4 increases the risk of cognitive impairments following various challenges while epsilon2 provides relative protection. ApoE4 is the major known genetic risk factor for late-onset Alzheimer's disease (AD).

Objective: To study the effect of hApoE4 and age on learning and memory of mice

Methods: We used hApoE4 transgenic (4 and 12 months) and age-matched C57BL/6 mice. Morris Water Maze (MWM) tests were performed to evaluate the spatial learning and memory. Immunohistochemistry was applied to detect oxidative stress and apoptosis.

Results: MWM demonstrated an age-related impairment in escape latency (30.0 ± 21.9 s vs. 27.3 ± 18.1 s, $p < 0.01$) and hidden platform test ($30.6 \pm 10.1\%$ vs. $43.1 \pm 12.4\%$, $p < 0.05$) in 12-month-old hApoE4 transgenic mice. There was no difference between 12-month-old and 4-month-old of C57BL/6 mice. This was consistent findings in oxidative stress.

Conclusion: The double effects of E4 and aging cause cognitive impairment. This effect may be attributable to oxidative stress.

EARLY AND LONG TERM ADMINISTRATION OF 17 β - ESTRADIOL AND GENISTEIN PREVENT AGAINST A β PLAQUE FORMATION IN APP TRANSGENIC MOUSE LACKING ENDOGENOUS ESTROGEN SYNTHESIS. Cao P, Yue X, Lancaster T, West-Liu M, McAllister C, Li R. Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

Background: Alzheimer's disease (AD) is the second-leading cause of dementia-related deaths in US. While extensive effort in investigating the causes and potential treatments for AD, we have focused on finding ways to prevent AD. Multiple preventive measures-mental stimulations, exercise, and a variety of dietary approaches-have been suggested, but their value in delaying the onset and/or reducing the severity of decline or disease is unclear. Questions still remain as to how the presence of certain conditions, such as estrogen and phytoestrogen therapy, may influence an individual's risk of Alzheimer's disease.

Methods: With increasing interest in hormone replacement therapies (HPT) in postmenopausal women and concerns of the balance between beneficial and side effects of HPT, here, we examined the effect of various estrogen treatments on AD neuropathology in an estrogen-deficient transgenic animal model of AD, APP23 transgenic mice with depletion of endogenous estrogen synthesis (APP23/Ar+/-). Female animals received continuously treatments of 17 β -estradiol, 17 α -estradiol, genistein or black cohosh for 3 and 9 months, respectively. Various neuropathological measurements were performed at end of the treatments, such as analyses of brain amyloid plaques, beta amyloid levels, beta-secretase activities and cognitive function.

Results: Our studies showed that early and long term treatment of 17 β -estradiol and genistein caused a significant reduction of brain plaque density compared to placebo treatments. In contrast, no change of plaque pathology was observed in the APP23 transgenic mice after 17 α -estradiol or black cohosh treatments regardless. There is no significant effect of late and short term estrogen treatments. Early estrogen treatment also prevented cognitive function impairment in APP23/Ar+/- mice.

Conclusion: Our results suggest that estrogen treatments might help to prevent AD pathologies in women when early and long term usage of 17 β -estradiol and genistein were taking place. No advantage of estrogen treatments in treating AD when brain has formed AD-liked neuropathology.

ROLE OF COMPLEMENT RECEPTOR 1 (CR1) IN ALZHEIMER'S DISEASE. Grover A, Mastroeni D, Whiteside C, Delvaux E, Huentelman M, Leonard B, Coleman PD, Rogers J. Banner Sun Health Research Institute; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Background: A recent genome-wide association study (GWAS) published in *Nature Genetics* found that single nucleotide polymorphisms (SNPs) in CR1 exhibited the third highest association with genetic risk for Alzheimer's disease (AD) ($P = 3.7 \times 10^{-9}$), following only apolipoprotein E (ApoE) and ApoJ. A significant CR1 SNP association ($P = 9.2 \times 10^{-6}$) was also observed in a second, independent GWAS report in the same issue. Notably, however, CR1 is poorly expressed in brain. Instead, its major roles are regulation of spontaneous complement activation and clearance of pathogens and immune complexes in the peripheral circulation. In these contexts, CR1 SNPs have already been identified that alter structure, expression, and function of the CR1 protein and appear to play pathogenic roles in other diseases.

It is now clear that amyloid β peptide ($A\beta$) moves from the CNS to the CSF and peripheral circulation, but its fate thereafter in primates appears to have been completely ignored. This is unfortunate since failure to clear $A\beta$ from the circulation would presumably set up a gradient that inhibited its clearance from brain. Moreover, attempts to immunize against $A\beta$ would immediately induce elevated $A\beta$ /anti- $A\beta$ immune complexes in the blood. Failure to clear elevated levels of immune complexes is well known to cause immune complex disorders, including vascular inflammation similar to that which killed a number of $A\beta$ immunized patients.

Methods: We have begun an examination of the genomics, physiology, and ultrastructure of CR1 in AD, mild cognitive impairment (MCI), and non-demented elderly control (ND) subjects using haplotype analyses, binding assays, and electron microscopy.

Results: We have identified a major new block of CR1 SNPs that exhibit significant linkage disequilibrium (LD) within the CR1 gene. The major haplotype variant, which we have termed H1, has a frequency of ~82%. A minor haplotype variant, H2, has a frequency of ~14%. In addition, the analysis identified a set of SNPs on the H1 background where the minor alleles are in significant LD, creating a subvariant of the H1 haplotype, H1b, that occurs in approximately 20% of the population.

Conclusions: These findings may be significant with respect to previous CR1 GWAS reports for two reasons. First, both the AD haplotype found in the GWAS research and the H1b subvariant share an ~20% frequency in the population. Second, the four CR1 SNPs identified in the GWAS reports are included in the set of SNPs that define the H1b subvariant. However, the original four GWAS SNPs were in non-coding regions, whereas one of the six H1b subvariant SNPs is within the coding sequence for the CR1 gene. For these reasons, we believe it is highly possible that the H1b subvariant is the gene variant giving rise to the association of CR1 with AD.

In primates, some 80% of the body's CR1 is expressed by circulating erythrocytes, which use CR1 to bind and clear pathogens and immune complexes. Our studies clearly demonstrate that $A\beta$ is subject to this potent clearance mechanism, and that AD erythrocytes are significantly deficient in their ability to capture circulating $A\beta$ compared to ND erythrocytes, with MCI erythrocytes exhibiting intermediate values. Electron microscopy also revealed $A\beta$ co-localized with erythrocytes and Kupfer cells in the hepatic sinusoids. Kupfer cells strip CR1-bound pathogens and immune complexes from erythrocytes and degrade them.

Poster 12

NOVEL MECHANISMS OF NEUROGENESIS IN ALZHEIMER'S MOUSE MODEL. He P, Staufenbiel M, Shen Y. Banner Sun Health Research Institute; Novartis Pharm Ltd., Basel, Switzerland; Arizona Alzheimer's Consortium.

Background: The notion of neurogenesis occurring in the brains of patients affected with Alzheimer's disease (AD) is widely discussed and very controversial. Neurogenesis, in adults, can take place in two regions of the brain: the subventricular zone, and the subgranular zone which is part of the hippocampus and also the region of our focus.

Methods: In this region, we investigated AD transgenic APP Swedish mutation (APP23) mice, to observe what effect overproducing the amyloid β protein ($A\beta$), had on hippocampal neural precursor cells (NPCs).

Results: We found dramatic decrease in the number of NPCs present in APP23 mice at 12 and 24 months of age. Hedgehog (Shh) signaling is responsible for regulating adult stem cells involved in the maintenance and regeneration of adult tissues. We explored the possible roles of the signal molecules have in cell proliferation. Meanwhile, glycogen synthase kinase 3 β (GSK-3 β) was found to be significantly promoted. A similar change was observed in the hippocampus from the brains of AD patients. Exposure of wild type hippocampal NPCs to aggregate $A\beta$ 1-42 was found to promote GSK-3 β level and new molecular targets are identified.

Conclusions: These results indicate that an impaired Ptc signaling is associated with a reduced hippocampal neurogenesis in AD brains.

INTRACRANIAL ATHEROSCLEROSIS AS A CONTRIBUTING FACTOR TO ALZHEIMER'S DISEASE DEMENTIA. Kokjohn TA, Maarouf CL, Sabbagh MN, Belohlavek M, Garami Z, Beach TG, Roher AE. Banner Sun Health Research Institute; Midwestern University; Mayo Clinic Arizona; Methodist Hospital, Houston; Arizona Alzheimer's Consortium.

Background: A substantial body of evidence amassed from epidemiologic, correlative and experimental studies strongly associates atherosclerotic vascular disease (AVD) with Alzheimer's disease (AD). Depending on the precise interrelationship between AVD and AD, systematic application of interventions to maintain vascular health and function as a component of standard AD therapy offer the prospect of mitigating what is presently the inexorable course of dementia. To assess this hypothesis it is vital to rigorously establish the measures of AVD that are most strongly associated with an AD diagnosis.

Methods: A precise neuropathological diagnosis was established for all subjects using a battery of genetic, clinical, and histological methods. The severity of atherosclerosis in the circle of Willis (CW) was quantified by direct digitized measurement of arterial occlusion in postmortem specimens and compared between AD and non-demented control (NDC) groups by calculating a corresponding index of occlusion.

Results: Atherosclerotic occlusion of the CW arteries was more extensive in the AD group than the NDC group. When compared to NDC, our multivariate regression models clearly indicate a link between the degree of atherosclerosis of the CW and AD (adjusted odds ratio: 1.06 (95% CI = 1.02-1.11, $p = 0.006$). Statistically significant differences were also observed between control and AD groups with regard to Braak stage, total plaque score, total NFT score, total WMR score, brain weight, MMSE scores and apolipoprotein E allelic frequencies.

Conclusions: Our results, combined with a consideration of the multifaceted impacts of impaired cerebral circulation, suggest an immediate need for prospective clinical trials to assess the efficacy of AD prevention using anti-atherosclerotic agents and interventions.

DEPLETION OF ESTROGEN RECEPTOR- β CONTRIBUTES TO ALZHEIMER'S DISEASE PATHOGENESIS IN FEMALES BY IMPAIRING MITOCHONDRIAL FUNCTION. Long J, Bowers A, McAllister C, Li R. Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

Background: Mitochondria are the major source of energy for the normal functioning of brain cells. Increasing evidence suggests mitochondrial oxidative damage might be one of early events in Alzheimer's disease (AD) progression. Estrogen has been shown to suppress mitochondrial oxidative stress, regulate energy metabolism, and regulate the expression of mitochondria-involved anti-apoptotic proteins like bcl-2 family and bcl-xL, which suggests that brain mitochondria may be major targets of estrogen action in the central nervous system. Studies also demonstrated that many of these protective effects can be blocked by an estrogen receptor (ER) antagonist, ICI-182780, suggesting an ER-mediated mode of estrogen action. Even more interestingly, recent reports have confirmed the localization of ER β in the mitochondria and suggested that estrogen can directly affect mitochondrial function through mitochondrial ER β mtER β).

Methods: To address whether female AD brains exhibit mitochondrial impairment and whether it is correlated with estrogen receptors, we conducted mitochondrial functional analyses in female AD patients and age-matched non-demented (ND) individuals. Using frontal cortex samples from the brains of age-matched AD and non-ND women, we examined mitochondrial cytochrome C oxidase (COX) activity, and reactive oxygen species (ROS)-induced intracellular protein oxidation as protein carbonylation along with receptor- β (ER β) subcellular distribution and protein expression. In order to investigate whether lacking of ER β causes mitochondrial dysfunction, mice with ER β gene knockout were used as an animal model.

Results: First, we found that the frontal cortices of female AD patients exhibited significantly reduced ER β expression, including in mitochondrial fraction, reduced mitochondrial COX activity, and increased protein carbonylation compared to the samples from ND. A significant linkage between the mitochondrial ER β expression and mitochondrial COX activity were observed in the female human brain, suggesting an involvement of ER β in mitochondrial function in the brain. Second, we noticed that mitochondria from the brains of ER β – knockout mice exhibited increased ROS generation and reduced mitochondrial membrane potential (MMP) under β -amyloid (A β ₁₋₄₂ or A β ₂₅₋₃₅) insult compared to brain mitochondria from wild-type control mice. These results suggest that ER β depletion can impair mitochondrial function in mice and may significantly contribute to the mitochondrial dysfunction involved in AD pathogenesis in women.

Conclusion: Although further investigation is needed, our novel detection of ER β expression in neuronal mitochondria in the female human brain along with the direct correlation of mtER β expression with COX activity and the significant decrease of mtER β in the AD brain suggest a possible connection between ER β and mitochondrial dysfunction in AD. This hypothesis is supported by our experiments involving transgenic ER β knockout mice, which showed that ER β deficiency leads to mitochondrial dysfunction in the brain by decreasing MMP and by increasing mitochondrial vulnerability to A β -induced ROS generation. Together, the results of this study indicate that ER β deficiency may play an important role in AD pathogenesis in females by contributing to mitochondrial dysfunction.

RECEPTOR FOR ADVANCED GLYCATION ENDPRODUCTS IN ALZHEIMER'S DISEASE: FROM BRAIN TO BLOOD. Lue L-F, Zhong Z, Moses GSD, Walker DG. Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

Background: Two major forms of receptor for advanced glycation endproducts (RAGE) play important roles in Alzheimer's disease (AD). The full-length cell-surface RAGE (fl-RAGE) mediates amyloid beta-induced oxidative stress, inflammatory responses, and neurocytotoxicity, whereas soluble forms of RAGE (sRAGE) antagonize the effects of fl-RAGE by preventing ligands from activating fl-RAGE. Previously we have studied fl-RAGE and sRAGE in human brain tissues and blood vessels (Lue et al., 2005 and 2001), RAGE transgenic mouse models (Fang et al., 2010, Arancio et al., 2004), and human cell culture models (Lue et al., 2001 and 2005). We are currently investigating the regulatory roles of sRAGE in blood. Our long term goal is to understand the regulatory mechanisms of fl-RAGE and sRAGE in the brain and the blood cells. As a naturally present, anti-inflammatory protein in the circulation, abnormal changes during early process of AD may alter the regulation of fl-RAGE and sRAGE production, which eventually may lead to compromised anti-inflammatory function of sRAGE.

Methods: In order to maintain normal function and the levels of sRAGE during ageing and AD, we proposed to test several herbal supplements to determine their effects on increasing production of sRAGE in animal models of AD. Proprietary herbal supplements formulated by our collaborator Dr. Hua from Beijing Chinese Medical University, were provided to us for this study. Transgenic mice (APP/PS1) were treated 6 days a week with placebo or supplements mixed with regular chow starting from 3 months of age for three months. Mice were sacrificed to determine their effects on RAGE expression, amyloid beta peptide load, and inflammation.

Results: We find that there was no difference in total sRAGE expression in cortical and hippocampal tissue homogenates after three months treatment. Further analysis will be performed to determine the effects on the fl-RAGE expression. At this point, our regime did not alter amyloid beta load analyzed by ELISA in unfractionated tissue homogenate. We are in the process of analyzing the levels of synaptophysin, glial fibrillary acidic protein (GFAP), and microglia using IBA1 marker. We anticipate anti-inflammatory effects from these supplements on glial responses.

Conclusions: This study is the first attempt to screen herbal supplements effective for sRAGE production. However, if supplements reduced fl-RAGE expression but not sRAGE, they could still be considered to have positive effect. Our goal is to discover natural agents that can modify disease course of AD by maintaining optimal amount of circulating sRAGE.

Poster 16

MICROGLIA ACTIVATION IN HEART FAILURE AFTER MYOCARDIAL INFARCTION IN RATS. Mutlu N, Gaballa M. Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

Background: Microglia activation is the hallmark of neuroinflammation. The activated microglia releases large amounts of inflammatory cytokines such as TNF- α , IL-1 β , and reactive oxygen species such as nitric oxide, which in turn could contribute to neuroinflammation and neurodegeneration. However, no data is available regarding possible microglia activation in heart failure after myocardial infarction (MI).

Methods: We created an experimental model of a heart failure after myocardial infarction (MI) by ligation of the left ascending descending coronary artery in rats. We also created a model of cerebral blood flow reduction by occlusion of either a single or both carotid arteries in rats. Microglia activation was assessed using both immunohistochemistry and western blot analysis of rat brain tissue.

Results: We showed that microglia was activated in the (white matter tracts) hippocampus and frontal cortex regions in both acute MI (1 day after MI) and in chronic heart failure (21 days after MI). However, the degree of activation is diminished in the chronic heart failure model compared to the acute MI. Inflammatory cytokines released from the injured myocardium with acute MI may be the trigger for the observed microglia activation. In contrast, in compensated heart failure, the inflammation is usually subsided, and cerebral hypoperfusion due to decreased cardiac output is commonly observed. Cerebral hypoperfusion, may trigger microglia activation. Therefore to determine whether or not hypoperfusion plays a role in microglia activation, we are examining microglia activation in a single and double carotid occlusion model in rats.

Conclusion: Thus, microglia is activated in both acute MI and heart failure, and inflammation and/or hypoperfusion is the mechanism of this activation in heart failure.

ANTI-STROKE HERBAL MEDICINE FOR ALZHEIMER'S DISEASE. Nural HF, Hua Q, Li R, Li P, Shen Y. Banner Sun Health Research Institute; Beijing University of Chinese Medicine; Arizona Alzheimer's Consortium.

Background. The pathological hallmark of Alzheimer disease, senile plaques are composed of Amyloid-beta ($A\beta$), which is generated from amyloid precursor protein (APP) by enzymatic digestion involving β - and γ -secretase. Abnormal processing of APP leads to AD-like pathological changes including increased β -secretase (BACE1) levels, $A\beta$ production and neurodegeneration. The role of BACE1 in abnormal APP processing makes it an important target in developing effective therapeutics for the treatment of AD.

Methods. In search of effective modulators/inhibitors of BACE1, we tested whether anti-stroke medicine, TongLuoJiuNao (TLJN) could affect APP processing via modulation of BACE1 *in vitro*. Here we show that TLJN reduces the $A\beta_{40}$ and $A\beta_{42}$ levels in Swedish mutant APP transfected HEK293 and neuronal hNT2 cells by reducing levels and activity of BACE1.

Results. We observed reduction in the levels of two components of the γ -secretase complex, PS-1 and Pen-2. Thus, TLJN's inhibitory effect on $A\beta_{40}$ and $A\beta_{42}$ could be mediated by its effect on the activities of β - and γ -secretase.

Conclusions. These findings suggest that anti-stroke drug TLJN have promising potential as a new drug in treatment of Alzheimer disease.

Poster 18

LONG-TERM LOW-DOSE DIETARY CHOLESTEROL ADMINISTRATION ON TAU LEVELS IN BLOOD AND BRAIN, AND AT8 STAINING IN THE BRAIN. Sparks DL, Martin T, Ziolkowski. Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

Background: Pioneering autopsy studies revealed a possible link between coronary artery disease, cholesterol and Alzheimer's disease (AD). In the cholesterol-fed rabbit model of human coronary artery disease we identified numerous neuropathologic features of AD including central accumulation of amyloid beta ($A\beta$) and cognitive deficits compared to rabbits fed unaltered diet.

Methods: Early studies were performed in animals administered a diet containing 2% cholesterol and tap water for only 8 weeks compared to animals administered normal rabbit chow and tap water for a similar length of time. Further studies suggested that the induction of AD-like $A\beta$ neuropathology by dietary cholesterol was found to depend on the quality of water the rabbit was drinking. Rabbits fed 2% cholesterol that had been drinking distilled water showed minimal AD-like neuropathology, whereas animals drinking tap water were severely affected. Subsequent studies indicated that it was the copper in the tap water that produced the difference in severity of the cholesterol-produced AD-like $A\beta$ pathology. It was clear that cholesterol caused the over-production of $A\beta$ in the brain and copper influenced its clearance to the blood.

Results: In our previous studies we administered 2% cholesterol and varying qualities of drinking water – ranging from local tap water to distilled water – and we were able to manipulate Alzheimer-like amyloid beta accumulation and memory deficits in less than 3 months but were unable to identify any changes in tau as the major component of the other characteristic lesion in AD – the neurofibrillary tangle (NFT). We performed a pilot study of 5 female animals on a 1% cholesterol diet and administered distilled water (n=2) compared normal chow animals on tap water (N = 2). We found that there were increased levels of tau and NFT-like lesions produced by 5 months of 1% cholesterol diet.

PRODUCTIVE VARIABLES IN FEMALES MIGHT ALTER COGNITIVE FUNCTION DURING AGE – STUDIES OF SPATIAL MEMORY IN FEMALE MICE. Walker A, Bowers A, Li R. Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

Background: Aging is associated with a decline in ovarian hormones, reproductive viability, and cognitive functions in both human and rodents. Studies showed that ovarian hormone elevations might enhance learning/memory. Because pregnancy is associated with increases in steroids for longer periods than are seen over the regular estrous cycle, we hypothesized that females with multiparity might have better learning/memory compared to that in virgin females. The enhancement of cognitive function in receptive females compared with non-receptive (virgin) females might be due to prior steroid exposure during pregnancy.

Methods: Female mice were divided into four groups: receptive (breeders with 1-3 litters), and non-receptive (virgin). Animal from each group were tested at age of 6 and 12 months, respectively. All animals were tested for spatial memory by Barnes maze. The mice begin the maze by sitting in a dark chamber for 30 seconds, before exploring to a bright light. During the first 4 days, each mouse had three minutes to find the target hole which connected an escape chamber as known as training trials. On day 5 and 12, the mice were tested for 90 seconds with the escape hole blocked as the short-term and long-term probe trials, respectively. The primary latency, total latency, poke frequency, primary errors and total errors were recorded for all the trails.

Results: There was a significant difference in the spatial memory behavior between receptive and non-receptive mice. At age of 6 months, the receptive mice showed shorter primary latency than that in non-receptive mice on Day 5 probe trail (short-term memory) only. In contrast, at older age (12 months old), the biggest differences between receptive and non-receptive mice were observed on Day 12 probe trail (the long-term memory). The non-receptive mice at age of 12 months took longer time to find the target hole, such as on average of 4.3 folds increase in time compared to that in age-matched receptive mice. This trend was also seen on the short-term probe trail, although no statistical significances were reached. In addition the twelve months receptive mice showed a Poisson distribution for both short- and long-term probe trails, while the age-matched virgin mice only displayed the similar distribution on the short-term probe trial.

Conclusions: Our studies showed that aged female mice with history of pregnancy and parity had better spatial learning/memory performance than those age-matched virgin mice. The differences between receptive mice and virgin mice were found more obviously in long-term memory at 12 month old and short-term memory at 6 month old. Our data are of particular interest because they suggest that a prolonged exposure to steroids can have long-lasting (even life-long) effects on cognition.

REGULATION OF ANTI-INFLAMMATORY MOLECULES CD200, CD200R, AND SUPPRESSORS OF CYTOKINE SIGNALING IN HUMAN NEURONS AND MICROGLIA.

Walker DG, Lue L-F. Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

Background: The brain has unique capacity to defend against damaging and uncontrolled inflammation. However, recent findings show that these systems are deficient with aging and with neurodegenerative diseases. CD200 is a ligand for CD200 receptor (CD200R); interaction of these two molecules activates anti-inflammatory signaling in CD200R expressing cells (inflammatory mediating cells). Another significant class of molecules is the suppressors of cytokine signaling (SOCS), which can also inhibit proinflammatory cytokines. The expression and regulation of these molecules in human brain-derived cells has not been extensively investigated. As inflammation can play a significant role in the pathology of Alzheimer's disease, but traditional anti-inflammatory drugs have failed to be effective, increasing the expression and function of endogenous anti-inflammatory molecules offers a novel therapeutic approach.

Methods: Expression of CD200 and SOCS was investigated in a unique human neuron system, namely hN2 differentiated neurons derived from neuronal progenitor cells. These cells have most features of primary human neurons. Expression of CD200R was investigated in human brain derived microglia. RNAs from cytokine-stimulated cells were used to study expression of these genes using real time polymerase chain reaction methodology.

Results: This project showed that CD200 mRNA expression in human hN2 neurons was not induced by the anti-inflammatory cytokines interleukin-4 (IL-4) or interleukin-13 (IL-13). This is contrary to findings by others using neurons derived from mice and shows a species specific response. No other tested cytokines had a significant effect on neuronal CD200 expression. By contrast, we have shown that CD200R expression by human microglia was strongly stimulated by IL-4 and IL-13, while no other cytokines had significant inhibitory or stimulatory effects. Studies of all SOCS genes (SOCS-1-7) have been carried out in this unique neuronal cell system. SOCS-1 and SOCS-3, the major modulators of STAT mediated cytokine signaling are strongly expressed by hN2 neurons, however SOCS-1 mRNA expression was induced by interferon gamma, while this cytokine had no effect on SOCS-3 expression. The features of these unique human brain cells will be presented as cellular models for studies of human diseases.

Conclusions: It has been suggested that augmenting CD200 by using IL-4 is a therapeutic strategy for brain diseases with an inflammatory component. These conclusions from rodent studies have not been confirmed in our studies using human cells. Based on our current and earlier studies, we conclude that augmenting CD200R with IL-4 is a better therapeutic strategy for aging neurodegenerative diseases with inflammatory components. We will discuss the possible interactions of CD200/CD200R and SOCS systems in human brain.

INHIBITION OF MARCKS PHOSPHORYLATION IMPROVES WORKING MEMORY. Allen AN, Talboom JS, Bimonte-Nelson HA, Broughton NS, Hackett NJ, Scheldrup MR, Engler-Chiurazzi EB, Huentelman MJ. Translational Genomics Research Institute; Arizona State University; Arizona Alzheimer's Consortium.

Background: We previously showed that the peripheral administration of a rho-associated protein kinase (ROCK) inhibitor improved learning and working memory in the aged rat. Myristoylated alanine-rich C-kinase substrate (MARCKS) is one of the downstream targets of the RhoA/ROCK pathway and is known to participate in several key neuronal cell functions including neurite outgrowth and growth cone adhesion. Therefore, we utilized a peptide-based MARCKS phosphorylation decoy strategy to investigate its role on memory performance in the aged rat model of cognitive decline.

Methods: We delivered a fusion peptide encoding the TAT protein transduction domain and residues surrounding two known serine phosphorylation targets (Ser152 and 156) within MARCKS (TAT-MARCKS) to seventeen-month-old Fischer-344 male rats at a dose of 1mg/kg/day (n=9). Control animals of the same age were treated with the peptide vehicle (saline, n=9). Dosing was initiated three days prior to behavior testing and continued throughout the experiment until sacrifice. Spatial working memory was assessed using water-escape versions of the plus maze and the radial-arm maze. Following sacrifice, the left hippocampus was utilized for genome-wide expression profiling.

Results: Behavioral results demonstrated that TAT-MARCKS treatment enhanced working memory performance in both mazes (plus maze: $t(16)=4.91$; $p<0.05$ and radial arm maze: $t(16)=4.38$; $p<0.05$). In addition, significant gene expression changes were noted for transcripts involved with learning, memory, neuronal plasticity and neuronal migration. These included Adcyap1 (FC=1.5; $p=0.029$), Tiam1 (FC=-1.5; $p=0.028$), and Filip1 (FC=-1.75; $p=0.032$).

Conclusions: Our data suggest that the partial blockade of MARCKS phosphorylation by way of a decoy peptide can enhance working memory. These results further support a role for MARCKS in the process of working memory and suggest that this may be able to be exploited for the development of novel cognitive enhancing agents. Further understanding of the interaction between MARCKS and the differentially expressed transcripts we noted may provide further insight into the biology of working memory in the aged rat.

IDENTIFICATION OF MULTIPLE NOVEL REGULATORS OF ALZHEIMER'S DISEASE (AD) RELATED TAU HYPERPHOSPHORYLATION. Frost D, Robeson RH, Brautigam GR, Azorsa D, Dickey C, Beaudry C, Meechovet B, Basu G, Holz D, Hernandez J, Bisanz K, Gwinn L, Grover A, Rogers J, Reiman EM, Hutton M, Stephan DA, Mousses S, Dunckley T. Translational Genomics Research Institute; University of South Florida; Banner Sun Health Research Institute; Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.

Background: Microtubule associated protein tau (MAPT) is hyperphosphorylated in Alzheimer's disease (AD) and aggregates in susceptible neurons as insoluble neurofibrillary tangles (NFTs). NFT formation is a central neuropathological feature of AD that is highly correlated with the severity of dementia. NFTs result in large part from increased phosphorylation of the microtubule stabilizing protein tau at certain AD-related residues. Identifying the kinases involved in the pathologic phosphorylation of tau may provide promising targets at which to aim new AD-modifying treatments.

Methods: We have screened 572 human kinases using a loss of function, high-throughput RNAi approach to identify kinases that contribute to AD-related tau phosphorylation.

Results: We show data implicated 7 kinases in tau phosphorylation at the AD-related threonine 231, 12E8 (serine 262/serine 356), and serine 396 epitopes. We further show that pharmacologic inhibition of three kinases, dual-specificity tyrosine-(Y)-phosphorylation regulated kinase 1A (Dyrk1A), and Rho-associated, coiled-coil containing protein kinase 1 (ROCK), and brain creatine kinase (CKBB) leads to decreased expression of phosphorylated tau protein.

Conclusions: The kinases identified here, as well as the small molecule inhibitors that target them, provide new candidates for therapeutic intervention to decrease the production of the pathologically phosphorylated forms of tau protein that have been implicated in neurodegeneration of Alzheimer's disease and other tauopathies.

INDUCTION OF PLURIPOTENT STEM CELLS FROM AUTOPSY-DERIVED FIBROBLASTS. Hjelm BE, Sue LI, Beach TG, Van Keuren-Jensen KR, Huentelman MJ, Craig DW. Translational Genomics Research Institute; Arizona State University; Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

Background: Human induced pluripotent stem (iPS) cells were first described in the scientific literature in November 2007 by two independent investigators, Yamanaka and Thompson. These groups demonstrated that human adult somatic cells could be “reprogrammed” to a pluripotent state (iPS cells) through the integrated expression of four stem cell-specific genes. IPS cells can subsequently be differentiated *in vitro* into a multitude of cell types found in all three germ layers. Dermal fibroblast cells propagated from live skin biopsies have become a common resource for iPS cell derivation and subsequent lineage-specific differentiation. We describe dermal fibroblast and iPS cell lines derived from donors enrolled in a whole-body autopsy program up to 97 years of age at the time of death.

Methods: Punch biopsies (3mm & 5mm) were collected from autopsy donors enrolled in the Sun Health Research Institute whole-body donation program. Primary dermal fibroblasts were cultured using a modified protocol from Villegas and McPhaul (2005). Autopsy donor-specific fibroblasts were infected with a lentivirus (Allele Biotechnology; MOI 20) containing Oct-4, Sox-2, c-Myc and Klf-4. Infected fibroblasts were transferred to Matrigel matrix 1 week post transduction, and iPS colonies were picked manually on days 25 and 32. These iPS cells were cultured in mTeSR1 media (Stem Cell Tech.). Fibroblasts lines were evaluated by brightfield microscopy (Wright-Giemsa stain) and immunocytochemistry (CD13, SSEA-3, DAPI). IPS cells were analyzed by brightfield, phase contrast, and immunocytochemistry (SSEA-3, SSEA-4, DAPI). *In vitro* pluripotency of iPS clones was evaluated using the StemPro® EZChek Human Tri-Lineage Multiplex PCR Kit, following 10-day and 20-day embryoid body cultures.

Results: Primary cell lines exhibited fibroblast morphology and robust CD13 expression, while a subpopulation of cells expressed SSEA-3. Primary dermal fibroblasts obtained from autopsy donors 1 and 2 were successfully reprogrammed into iPS cells. These iPS cells derived from postmortem tissue express the stem cells surface markers SSEA-3 and SSEA-4, in addition to the stem cell core transcription factor Oct-4.

Conclusion: To our knowledge, iPS cell-lines derived from post-mortem skin biopsies have largely not been described from individuals over the age of 80 in the scientific literature. We hypothesize that these autopsy-derived cells may be particularly useful for the investigation of age-related diseases and for the development of neurological disease models. In the future, our hope is to characterize neural cells differentiated from autopsy-derived iPS cells and effectively compare them to post-mortem brain tissue from the same individual.

P62 (SQSTM1) PLAYS A SIGNIFICANT ROLE IN REGULATING THE DEGRADATION OF TAU PROTEIN. McDonald B, Looyenga B, Robeson R, Meechovet B, Frost D, MacKeigan J, Dunckley T. Translational Genomics Research Institute; Van Andel Research Institute; Arizona Alzheimer's Consortium.

Background: Neurofibrillary tangles, composed of hyperphosphorylated tau protein, are one of the main pathological characteristics of Alzheimer's disease affected neurons and are highly correlated to dementia severity. We used a high-throughput, loss-of-function RNA interference assay to screen over 7,000 unique genes in order to identify proteins involved in the accumulation of pathologic forms of tau protein. The p62/sequestosome 1 (SQSTM1) protein emerged as a strong candidate. SQSTM1 functions as a shuttle for ubiquitinated proteins, gating degradation of the tagged proteins for proteasomal degradation or autophagocytosis. Here we test the hypothesis that decreased expression of p62 alters the flux of tau protein degradation through autophagic and proteasomal pathways, leading to a net decrease in tau protein levels.

Methods: We used a combination of p62 siRNA knockdown and inhibition or upregulation of autophagy and of the proteasome to test potential synergistic or antagonistic effects on the expression of tau protein. H4 neuroglioma cells constitutively overexpressing the 4R0N tau isoform were treated with either the proteasome inhibitors lactacystin and MG132 or the autophagy upregulator rapamycin in combination with p62 siRNA. Changes in total tau and phosphorylated tau were quantified by western blot.

Results: Knockdown of p62 expression decreased total tau by 40%, and multiple phosphorylated forms of tau, including pS396, pT231, and pS262 tau by 50-60%. p62 reduction also increased the levels of LC3B I, suggesting reduced autophagic activity. Inhibiting the proteasome to 14% of normal activity with MG132 increased phosphorylated tau levels and reduced the impact of p62 knockdown on several phosphorylated tau epitopes. Levels of p62 were also negatively correlated with proteasome activity. Autophagy upregulation decreases levels of both tau and p62.

Conclusions: Our combined results indicate that both p62 and tau are degraded both through the autophagic pathway and via the proteasome. Additionally, these results are consistent with p62 knockdown increasing the rate of tau degradation through the proteasomal pathway, rather than through autophagy. However, a pool of pathologically phosphorylated tau protein is clearly degraded through autophagy and pharmacologic manipulation of this pathway can reduce the accumulation of pathologic forms of tau. Manipulation of tau degradation pathways may provide an additional therapeutic target to help alleviate the burden of toxic tau aggregates in Alzheimer's disease affected neurons.

ROLE OF EIF2AK2 AND DYRK1A IN THE HYPERPHOSPHORYLATION OF TAU.

Meechoovet B, Robeson R, Frost D, McDonald B, Valla J, Dunckley T. Translational Genomics Research Institute; Barrow Neurological Institute; Arizona Alzheimer's Consortium.

Background: Neurofibrillary tangles (NFTs) are a hallmark pathological finding of Alzheimer's disease and result in part from the hyperphosphorylation of the microtubule stabilizing protein tau. Identifying kinases that are involved in the modification of tau phosphorylation may provide potential therapeutic targets. We have previously identified eukaryotic translation initiation factor 2 alpha kinase 2 (EIF2AK2) and dual-specificity tyrosine phosphorylation-regulated kinase 1A (DYRK1A) as modifiers of tau phosphorylation on threonine 231 and serine 262 epitopes. Two important questions resulting from those studies are (1) whether DYRK1A or EIF2AK2 directly phosphorylate tau protein and (2) with what additional proteins do EIF2AK2 and DYRK1A interact to impact tau phosphorylation? We have begun to address these questions through co-immunoprecipitation experiments and *in vitro* phosphorylation assays.

Methods: An N-terminally FLAG-tagged form of EIF2AK2 protein was overexpressed in H4 human neuroglioma cells that have also been engineered to overexpress 4R0N tau. The FLAG-EIF2AK2 protein was affinity purified and interacting proteins identified using a combination of SDS-PAGE and mass spectrometry. Active forms of purified DYRK1A and EIF2AK2 were used in *in vitro* phosphorylation assays with purified human recombinant tau protein to determine if either kinase directly phosphorylates tau protein.

Results: Several EIF2AK2 interacting proteins have been identified. The role of these proteins in tau phosphorylation remains to be clarified. *In vitro* phosphorylation assays indicate that DYRK1A and EIF2AK2 phosphorylate tau protein on epitopes detected by the anti-pS396 antibody, suggesting that serine 396 is phosphorylatable by both kinases *in vitro*. Data for additional phosphorylation sites are unclear owing to high levels of endogenous tau phosphorylation on those sites in the particular cell line from which tau was purified.

Conclusions: Our current findings show that inhibition of DYRK1A and EIF2AK2 causes decreases in phosphorylated tau isoforms and suggest that effects of each kinase on tau could result from direct phosphorylation. In addition, several EIF2AK2 interacting proteins could have functional roles in tau phosphorylation that are yet to be explored. Future studies to determine the role of EIF2AK2 and DYRK1A in tau phosphorylation include using known small molecule inhibitors against each kinase and overexpression of each kinase in primary neuronal cultures.

Poster 26

AGE EFFECTS ON NEURONAL ACTIVITY IN THE PERIRHINAL CORTEX. Burke S, Maurer AP, Nematollahi S, Wallace JL, Uprety A, Barnes CA. University of Arizona; Arizona Alzheimer's Consortium.

Background: Numerous studies have shown that normal object recognition requires an intact perirhinal cortex. The fact that this cognitive skill is altered by the aging process, suggests that the functional integrity of this structure may be altered across the lifespan. T

Methods: The current experiment investigated whether age-related deficits in stimulus recognition could be attributed to alterations in the underlying activity patterns observed in single perirhinal cortical neurons. Multiple single neurons in the perirhinal cortex were recorded simultaneously with 'hyperdrives' as 6 young (9 months old) and 6 aged (25-27 months old) rats traversed a circular track for a food reward. During some behavioral conditions the track was empty except for two food dishes in which reward was placed. During other conditions the track contained 8 objects evenly spaced around the track. During the first epoch of behavior, all 8 objects were novel. After completing 20 laps (10 clockwise and 10 counterclockwise), rats were allowed to rest for either 20 minutes or 2 hours. After this delay period, the rat returned to the track to run another 20 laps. During this second behavioral epoch, the track contained 6 familiar objects from the first behavioral epoch and 2 novel objects.

Results: During all behavioral conditions it was observed that, in both young and aged rats, a proportion of perirhinal cortical neurons exhibit increased activity at the locations of the food dishes ('food dish fields'). Additionally, when objects were on the track, a proportion of perirhinal cortical neurons in young and old rats showed increased firing at the location of objects ('object fields'). Importantly, the proportions of perirhinal cortical neurons showing food dish fields or object fields was significantly less in the aged compared to the young rats. Conversely, the proportions of perirhinal cortical neurons showing no activity during track running was significantly higher in the aged relative to the young rats.

Conclusions: The changes observed here in perirhinal cortical neuron activity patterns could contribute to the behavioral deficits that have been observed in old rodents and humans in object recognition tasks.

MAXIMAL ELECTRO-CONVULSIVE SHOCK INDUCED C-FOS mRNA EXPRESSION IS REDUCED IN THE HIPPOCAMPUS OF AGED RATS. Chawla MK, Penner MR, Olson K, Barnes CA. University of Arizona; Arizona Alzheimer's Consortium.

Background: Rapid and transient increase in immediate-early genes (IEGs) have been reported following electroconvulsive shock (Cole et al., 1990). Transcription of these genes regulates a cascade of subsequent genomic responses leading to long lasting changes in neuronal activity, morphology and receptor redistribution (Morgan and Curran, 1989). Previous studies have shown both an increase in c-fos mRNA following LTP (using high frequency stimulation) in fascia dentata of aged rats and a decrease in c-fos protein following seizure in aged mice (D'Costa et al., 1991).

Methods: To ascertain whether a brief electroconvulsive shock can elicit a differential response in aged animals we used fluorescence in situ hybridization and high-resolution confocal microscopy to obtain a measure of the numbers of cells that express c-fos mRNA and RT-PCR to measure the mRNA levels of c-fos. These data were obtained for the fascia dentata, and CA hippocampal sub-regions at 5, 30 and 60 min following maximal electroconvulsive shock treatment (MECS) in young and old rats.

Results: With one exception (pyramidal cells; 60 min following seizure), there were equivalent numbers of c-fos expressing cells following seizure treatment in young and old rats. There was no age difference revealed by RT-PCR analysis following resting behaviors in either pyramidal or granule cells. Aged animals, however, exhibited a two-fold decline in c-fos mRNA levels as measured by RT-PCR at 5, 30 and 60 min intervals in the granule cells and at 30 and 60 min intervals in the CA pyramidal cells.

Conclusions: While the consequence of reduced c-fos mRNA per cell in older animals, following seizure, remains unknown at present, it is possible that it is a compensatory or neuro-protective response. The beneficial or detrimental consequence of this age-related change remains to be investigated.

HIGH-RESOLUTION ANAMORPHIC ADAPTIVE SPECT IMAGING WITH SILICON DOUBLE-SIDED STRIP DETECTORS. Durko, HL, Barrett, HH, Furenlid, LR. University of Arizona; Arizona Alzheimer's Consortium.

Background: Recent advances in radiotracers for amyloid plaques, coupled with the development of suitable mouse models for Alzheimer's disease motivate the need for high-resolution small-animal brain imagers. Silicon-based devices are ideal for the detection of the low-energy gamma rays from iodinated radiotracers, and photolithographic fabrication techniques allow for the production of high-resolution double-sided strip detectors, in which the measurements of very large numbers of virtual pixels are read out by separate x and y position-sensitive electrodes.

Methods: An imaging system is being developed that consists of two sets of movable, keel-edged copper-tungsten blades configured as adjustable slits. These slits can be positioned independently between the object and detector, producing an anamorphic image in which the axial and transaxial magnifications are not equal. The detector is a 2" × 2", millimeter-thick 1024 × 1024 silicon double-sided strip detector with a 59- μ m strip pitch. A one-to-one magnification scout image is used to determine the optimal axial and transaxial magnifications, and the system is configured to magnify each object in such a way that an anamorphic image fills the detector in order to produce the highest-resolution projections. The system magnification and object position adapt with each projection in order to image the desired region of interest.

Results: We present preliminary results from this adaptive system and discuss calibration and acquisition methods.

PRE-ACTIVATION OF HIPPOCAMPAL CA1 ACTIVITY PATTERNS IS REDUCED IN OLD RATS. Glattig AF, Schimanski LA, Broersma BM, Barnes CA. University of Arizona; Arizona Alzheimer's Consortium.

Background: The hippocampus may play a role in the coordination of memory consolidation processes by reactivating sequences of cell activity (Wilson and McNaughton, 1994). Repetitive track running results in recurring pyramidal cell activity patterns, and cell pair correlations of firing between neurons during behavioral episodes are preserved in subsequent quiet waking and slow wave sleep. It is unknown, however, whether multiple episodes of similar behavioral experiences within the same day interact with the reactivation process.

Methods: Five young (9-12mo) and 4 old (26-28mo) Fischer 344 rats ran 35-40 laps for food reward on a circular track, and rested in a pot for 30-min before and after track running, while hippocampal area CA1 pyramidal cell activity was recorded. Rats ran two sessions per day (2-hr inter-session-interval) for 31 days in an environment that was not experienced prior to the first day of recording. For both the morning and afternoon recording period, the electrophysiological expression of the reactivation process was calculated using the explained variance method (Kudrimoti et al., 1999).

Results: When cell pair correlations from all rats over all 31 days were considered together, no differences in reactivation were observed between the first and second sessions within days. Additionally, as reported previously, we confirm that no differences are observed in explained variance in the rest period following the first session of the day between age groups (Gerrard et al., 2001). Greater “pre-activation”, however, was observed during rest before the second session of the day than before the first session of each day. To determine whether this effect changes as the environment goes from being novel to familiar, we examined correlations of firing patterns during days 1-3 versus days 11-13 of exposure to the environment. During days 1-3, pre-activation prior to the second session was significantly less in the old compared to the young rats. This reduction in pre-activation in old rats was not apparent by days 11-13.

Conclusions: These data suggest that 1) behavioral experience can affect activity pattern reactivation processes in CA1 for up to 2 hours in both young and old rats; and 2) that this pre-activation effect is attenuated in old compared to young rats for the initial days in which the rats are learning about a novel environment. This reduction in pre-activation in the old rats could reflect defective encoding processes in these spatial memory-impaired animals.

CHARACTERIZATION OF BEHAVIORALLY-INDUCED ARC EXPRESSION IN VENTRAL TEGMENTAL NEURONS DURING AGING. Hoang LT, Wann EG, Fellous J-M, Barnes CA. University Arizona; Arizona Alzheimer's Consortium.

Background: Dopaminergic neurons of the ventral tegmental area (VTA) have been shown to be highly correlated with reward. As rewards are thought to be central for predicting the outcome of future events which can guide behavior, possible changes in the reward system during aging might lead to impairments in cognitive or behavioral flexibility. We previously reported that the immediate-early gene (IEG) Arc is expressed in the VTA of young and aged male rats after exposure to a sexually receptive female rat, a behavior known to activate the VTA (Hoang et al., 2008). Although video-scored behavioral responses were similar across age groups, the proportion of Arc-expressing VTA neurons of aged animals was significantly attenuated in the rostral versus caudal regions of the VTA. IEG expression is thought to be dynamically regulated by specific forms of patterned synaptic activity that underlie information storage and plasticity. These results support the hypothesis that VTA plasticity is diminished over the lifespan. Because of the heterogeneity of cells in this region, it was important to further characterize those VTA cells that express Arc in the rostral versus caudal regions.

Methods: We used fluorescence in situ hybridization for tyrosine hydroxylase (TH) mRNA, a dopamine biomarker, and Arc mRNA to determine the distribution of neurons that co-express these markers in the VTA of young and aged rats.

Results: Behaviorally-induced TH mRNA expression was significantly attenuated in the rostral VTA of aged animals. Additionally, we found that Arc mRNA and TH mRNA co-localized only in the caudal region of the VTA, and that this co-localization is also reduced in aged animals. These results suggest that behaviorally-induced Arc expression in the VTA varies not only by cell type or location along the rostro-caudal axis of the VTA, but also during normal aging. Specifically, although TH+ neurons in the rostral VTA were activated for sexual behavior in young and aged animals, these neurons did not express Arc, and were not engaging the same molecular cascades known to be important for plasticity mechanisms in other brain regions such as the hippocampus. Conversely, TH+ neurons activated by sexual behavior in the caudal VTA largely expressed Arc, indicating that they may well undergo similar plasticity processes.

Conclusions: Given that dopaminergic afferents arising from different regions of the VTA project to different areas of the brain, these data may have important implications for the processing of reward and event salience. Furthermore, given that dopamine biomarkers are known to generally decline during normal aging, these data may provide insights into the specificity with which the VTA is altered over the lifespan.

FASTSPECT III: A THIRD-GENERATION HIGH-RESOLUTION DYNAMIC SPECT IMAGER. Miller BW, Moore SK, Barber HB, Trouard TP, Barrett HH, Furenlid LR. University of Arizona; Arizona Alzheimer's Consortium.

Objectives: FastSPECT III is a recently commissioned 20-camera small-animal SPECT imager designed specifically for imaging the rodent brain. High-resolution SPECT imaging of the rodent brain is of great interest for studying neurological pathologies, including Alzheimer's and Parkinson's disease. Many such studies have not been possible in the past due to resolution limitations of commercially available SPECT systems. FastSPECT III will provide SPECT imaging studies with isotropic linear resolution ~ 250 microns.

Methods: FastSPECT III represents the first stationary SPECT imager developed using high-resolution CCD-based gamma cameras called BazookaSPECT. Twenty BazookaSPECT detectors acquire projections of a spherical field of view with pinholes selected for desired resolution and sensitivity. Novel aperture and pinhole fabrication techniques were employed to produce custom imaging apertures. With real-time processing capabilities of graphics processing units (GPUs) and multi-core processors, the twenty cameras acquire and process data at 200 frames per second; $\sim 10^9$ pixels per second are processed.

Results: We recently completed the system integration of FastSPECT III. The first pinhole projection images of the system were acquired using a ^{125}I brachytherapy seed and are shown in the attached figure.

Conclusions: FastSPECT III is the first stationary SPECT imager based on BazookaSPECT detector technology. We have acquired the first projection images and dynamic pre-clinical imaging studies with real-time MLEM reconstructions will begin shortly.

DNA METHYLATION OF ZIF268 IS NOT DYNAMICALLY REGULATED WITHIN THE AGED HIPPOCAMPUS FOLLOWING SPATIAL BEHAVIOR. Penner MR, Roth TL, Lubin FD, Roth ED, Hoang LT, Sweatt JD, Barnes CA. University of Arizona; University of Alabama Birmingham; Arizona Alzheimer's Consortium.

Objectives: The neurobiological underpinnings of age-related memory deficits include aberrant changes in gene transcription that affect the ability of the aged brain to be “plastic.” Memory and synaptic plasticity processes are associated with transcription of immediate-early genes (IEGs), such as Arc (activity-regulated cytoskeletal gene) and zif268. Blocking the expression of these genes in adult animals prevents the consolidation of memory, and decreased IEG expression is observed as a result of the normal aging process. The molecular mechanisms underlying these changes in gene transcription are not currently known, but recent work points to DNA methylation as a potential novel mechanism. Epigenetic changes involving the covalent chemical modification of DNA by DNA methyltransferases, typically results in transcriptional silencing and loss of gene function, although transcriptional activation is also a possible effect. Regardless of whether silencing or activation of transcription results from this modification, DNA methylation can play a key role in dynamically regulating gene transcription in the adult CNS. In previous work we have observed significant age-associated changes in the DNA methylation status of the Arc gene (Penner et al., 2008) within the hippocampus (CA1 and the dentate gyrus).

Results: Here, we report that, like Arc, the DNA methylation status of the zif268 gene can be dynamically regulated by spatial behavior within the adult hippocampus. In area CA1 there is a significant reduction in methylation of the zif268 gene, whereas in the dentate gyrus, adult rats show a significant increase in methylation of zif268. In contrast to the adult animal, the DNA methylation status of the zif268 gene is not dynamically regulated following spatial behavior in aged rats. The absence of a dynamic change in the methylation status of zif268 within the aged hippocampus may contribute to the reduced levels of zif268 mRNA that have been previously observed. Moreover, because zif268 has been shown to play a key role in the maintenance of long-term memory, these changes are likely contribute to the memory deficits observed in aged animals.

AGE DIFFERENCES IN PERFORMANCE OF APPETITIVE INSTRUMENTAL TASKS.
Samson RD, Lipa P, Barnes CA. University of Arizona; Arizona Alzheimer's Consortium.

Objectives: Emotions differentially influence memory for learned items in old versus young adults. Specifically, older adults tend to remember items with a positive value more accurately than neutral or negative ones, whereas younger adults do not tend to remember positive items better than neutral or negative ones (e.g., Mather and Carstensen, 2005; Trends Cogn Sci.).

Methods: To investigate further the influence of emotions on learning, young (9-12 mo) and aged (24-27 mo) Fischer 344 rats were paired while performing a series of appetitive instrumental learning tasks. Rats were initially trained to press two different levers, one associated with maltodextrin and the other with sucrose. The performance levels of young rats were matched to levels in old rats, leading to a similar learning curve during training. In this training, the probability of obtaining a reward was gradually decreased to reach a random ratio (RR) probability of 20% at the end of 11 days. The effect of the change in the incentive value of the reward was then assessed in a reinforcer devaluation task using selective satiation.

Results: Both groups were sensitive to the devaluation of the outcome, lever pressing more for the non-devalued outcome. No differences were detected between age groups. Conversely, old rats were found to be generally more sensitive to the degradation of the action-outcome contingency as shown by a selective decrease in pressing to the degraded lever-outcome pair. In this contingency degradation task, one of the lever-outcome associations was degraded by also delivering rewards in the absence of actions (RR of 5%). Finally, old rats tended to extinguish lever pressing faster than did young rats in a subsequent extinction test involving the lever that was not previously degraded.

Conclusion: These data suggest that older rats are more sensitive to changes in reward contingencies and to the absence of reward following their actions. While the data do not necessarily suggest that old rats learn or adapt faster, it is possible that they are more prone to refrain from producing actions when they are not needed or when the reward is not readily available. Other experiments that have examined young and old rat behavior using extinction tests of aversive stimuli, have shown greater resistance to extinction in aged rats (e.g., Bevilaqua et al., 2008; Topic et al., 2008). However, these experiments were conducted under more stressful situations, which may explain the apparent differences between our studies. It will be interesting to extend the present experiment to different instrumental and Pavlovian situations to determine the degree to which the effects of aging on extinction learning can be generalized.

HIPPOCAMPAL CA1 FIRING RATES VARY WITH SPATIAL TRAINING AND PLACE FIELD STABILITY IN YOUNG AND OLD RATS. Schimanski LA, Broersma BM, Lipa P, Barnes CA. University of Arizona; Arizona Alzheimer's Consortium.

Objectives: Place fields expressed by hippocampal area CA1 cells collectively form an environment-specific representation ("map") that remains largely consistent after encoding. However, we found previously that a small proportion of CA1 cells exhibits changes in place field locations when spatial firing patterns are compared several hours apart. This led us to ask whether spatially "stable" and "unstable" place cells exhibit different firing rates, and whether the activity patterns of the cells are modified during learning. Considering the altered CA1 place cell properties and spatial memory impairments observed in aged rats (e.g., Barnes et al., 1997, *Nature*, 388: 272-5; Shen et al., 1997, *J Neurosci*, 17: 6769-82), the effect of age on the activity of stable and unstable place cells was also examined.

Methods: Six young (9-12 mo.) and 6 old (26-28 mo.) Fischer 344 rats were implanted with a multi-tetrode array to record the activity of ensembles of single cells in hippocampal area CA1. In a novel environment, rats ran 35-40 laps on a circular track for food reward twice daily for 31 days. During runs, rats were trained on a spatial version of classical eye blink conditioning in which they learned the locations of blink-inducing stimuli. Each run was flanked by 30-min rest periods, and rats were returned to their home cages for at least 2-hr between the two daily sessions. For each cell, spatial correlations were calculated between firing rates in bins along the circular track to quantify the stability of place fields between the sessions of each day.

Results: When data from all 31 days of training were considered together, no significant age differences were found in firing rates within pre- or post-run rests. However, young rats exhibited a higher firing rate during maze running early in training than did old rats, even when data were controlled for differences in running speed between age groups. This elevated firing rate in young rats declined as experience grew; during the last 10 days of training firing rate was comparable between age groups. Also, cells that exhibited a highly conserved spatial firing pattern between maze running episodes (spatially stable cells) exhibited a higher firing rate than did unstable cells while rats were running (i.e., running velocity > 5cm/sec), but not while rats were stationary on the track (0-5cm/sec); this effect was observed in both age groups for the duration of the experiment.

Conclusion: Reduced firing rates in spatially unstable CA1 cells during running suggest a lack of strong spatial input, perhaps enabling these cells to encode other cues that are unique to each running session. Although this pattern is seen in both age groups, higher firing rates are observed in young rats early in training. We speculate that these increased rates may be elicited by modulatory inputs that could be reduced in old rats. This may result in a reduced signal-to-noise ratio for encoding new spatial information in aged CA1 pyramidal cells.

HIPPOCAMPAL CA1 PLACE REPRESENTATIONS STABILIZE AS YOUNG AND OLD RATS GAIN EXPERIENCE IN A NOVEL ENVIRONMENT. Schimanski LA, Broersma BM, Lipa P, Barnes CA. University of Arizona; Arizona Alzheimer's Consortium.

Objectives: Place cells in hippocampal area CA1 exhibit increased firing rates in a particular region of an environment (i.e., place fields). These place fields form an environment-specific representation ('map') that remains consistent between exploration episodes. However, when exploring a familiar environment, aged rats sometimes exhibit global "remapping" such that most place field representations are mismatched between consecutive sessions (Barnes et al., 1997; *Nature*, 388: 272-275). We also know that place fields form during the first minutes an animal explores a novel environment and require NMDAR activity for long-term stability. These findings led us to ask whether gaining experience in an environment is associated with increased stability of place fields, and whether there are age differences in remapping as an environment transitions from novel to familiar.

Methods: In a novel environment, 5 young (9-12 mo) and 4 old (26-28 mo) Fischer 344 rats ran 35-40 laps on a circular track twice daily (2-hr inter-session-interval), during which activity of ensembles of single cells in hippocampal area CA1 was recorded. Firing rates were determined for each cell over all track locations, and spatial correlations were calculated to quantify the stability of place fields between the sessions of each day.

Results: While the majority of correlations between the two recording sessions within a day were strong, about 25% of cells in both age groups showed weak spatial correlations on the first day the rats experienced the novel environment. The proportion of cells with low correlations between sessions on a single day significantly decreased during days 1 to 13 from 23 to 6% in young rats and 24 to 11% in old rats. Interestingly, global remapping (defined as low spatial correlation in at least 70% of cells within a session) was not observed until day 14 in either age group.

Conclusions: In summary, place field representations of a novel environment stabilize in both young and old rats during two weeks of daily exposure to the environment. Increased stabilization includes both fewer cells expressing low spatial correlations, and more cells expressing high spatial correlations between sessions. The lack of global remapping until day 14 suggests that while initial representations of an environment are stabilizing, the formation of new ones may be inhibited.

A β ₁₋₄₂ AND THE ENDOCYTOSIS OF AMPA-TYPE GLUTAMATE RECEPTORS IN CULTURED HIPPOCAMPAL NEURONS. St. John PA. University of Arizona; Arizona Alzheimer's Consortium.

Background: Amyloid-beta (A β) peptides are the primary constituents of amyloid plaques in the brain in Alzheimer's disease (AD). A great deal of evidence supports the conclusion that A β peptides cause AD, but how they do so is not clear. A β peptides spontaneously aggregate, or self-assemble, to generate distinct macromolecular forms. In considering the range of molecular, cellular, and cognitive abnormalities observed in AD, in AD-model animals, and in neurons exposed to A β , it appears that different deficits may be caused by different assembly forms of A β , rather than all stemming from a single proximate cause. For example, recent evidence from our lab and others indicates that fibrillar forms of A β ₁₋₄₂ (A β 42) selectively activate apoptotic pathways in CNS neurons, that is, they may be considered "neurotoxic," while several groups have provided evidence that less aggregated, soluble forms of A β are more "synaptotoxic," that is, they more potently interfere with synaptic function, including synaptic plasticity, and even synaptic survival. This dichotomy of functional effects of different A β assembly forms is consistent with the suggestion that fibrillar and soluble forms of A β 42 bind to different subcellular locations and therefore different molecules on hippocampal neurons (St. John, 2007). A large and growing body of evidence indicates that the rapid trafficking of glutamate receptors onto and off of the neuronal surface plays a critical role in important forms of synaptic plasticity. It has been suggested that A β peptides interfere with synaptic plasticity – and possibly cause memory deficits in AD – by altering the normal dynamics of glutamate receptor trafficking in CNS neurons.

Methods: We have examined the effects of different assembly forms of A β 42 on the endocytosis of AMPA-type glutamate receptor subunits in cultured hippocampal neurons, using microscopic imaging to track and localize the internalized receptors (St. John and Gordon, 2001).

Results: Our results to date indicate that 1) A β 42 promotes the endocytosis of GluR1 subunits, but 2) interferes with the NMDA-induced endocytosis of those subunits; 3) oligomeric and fibrillar forms of A β 42 differ in their effects on NMDA-induced endocytosis of GluR1 subunits; and 4) oligomeric A β 42 does not show preference for binding to GluR1 subunits themselves.

Conclusions: Together with previous studies, these results support the hypothesis that different assembly forms of A β 42 cause different cellular/molecular deficits in AD.

LONGITUDINAL MAGNETIC RESONANCE SPECTROSCOPY AND T2 MEASUREMENTS IN A MOUSE MODEL OF NIEMANN-PICK TYPE C DISEASE. Totenhagen J, Borbon I, Yoshimaru E, Howison C, Erickson RP, Trouard TP. University of Arizona; Arizona Alzheimer's Consortium.

Objectives: Niemann-Pick Type C (NPC) disease is a rare autosomal recessive neurodegenerative disease which involves impaired transport of intracellular lipids and accumulation of unesterified cholesterol in lysosomes and late endosomes in cells throughout the body [1]. NPC disease symptoms, including progressive ataxia, developmental dystonia, and dementia, often appear in the first decade of life, and the disease is often fatal by the end of the patient's teenage years. No effective treatments are currently available, but several have been proposed and are in various stages of development and testing in animal models. Reliable and quantitative non-invasive imaging techniques that can track the progression and response to treatment of NPC disease will be valuable in both preclinical animal model studies and clinical studies.

Abnormal myelination has been reported in a case study of clinical NPC disease using Diffusion Tensor Imaging (DTI) [2]. Demyelination in a mouse model of NPC disease has been reported shortly after weaning at 23 days of age and quantified with DTI experiments [3], but required 3 hours of scan time. Magnetic resonance spectroscopy (MRS) has been used in studies of several mouse models of neurodegenerative diseases [4], and in clinical studies of Niemann-Pick Type C disease [5,6,7], but has not been reported in the NPC mouse model. In this work, a longitudinal study of T2 mapping and MRS measurements in a mouse model of NPC disease has been performed to examine T2 relaxation and brain metabolite levels as possible indicators of disease progression and response to therapy.

Methods: Quantitative T2 measurements and single voxel MRS were carried out on wild type and NPC mice at 23 and 67 days of age. Experiments were carried out on a 7T Bruker Biospec scanner equipped with a four element phased array receive-only surface coil. Animals were anesthetized with isoflourane gas, and body temperature monitored with a fiber-optic rectal probe and maintained at 37 °C.

T2-weighted datasets were collected with a 2D radial fast spin-echo sequence. A reconstruction method taking advantage of the oversampling of the center of k-space in radial sampling [8] was used to obtain eight images with varying TE values, and calculate T2 maps from 21 coronal slices within the brain. A region of interest analysis was used to obtain T2 values from the white matter areas of the external capsule, corpus callosum, and cingulum, while avoiding inclusion of ventricular spaces.

MRS datasets were collected with a point-resolved spectroscopy (PRESS) sequence, and the following acquisition parameters: TR=2500 ms, TE=20ms, 2048 points covering a spectral width of 4 kHz., and 250 averages for a scan time of 10:35 (min:sec). 3mm cubic voxels were placed in the cortex and cerebellum areas of the mice on which the FASTMAP shimming procedure was used. Spectra were analyzed by calculating the ratio of the metabolite peak signals to that of the unsuppressed water signal from the spectroscopic voxel.

Results: T2 values in white matter regions differed significantly between the WT and NPC groups at all time points studied. T2 relaxation times in both NPC and WT mice decreased with age. None of the MRS metabolite levels were significantly different between the two groups of mice. From these results, it is likely that quantitative T2 mapping could play a role in non-invasive evaluation of NPC disease and its response to therapy while MRS measurements, as performed, appear to lack the sensitivity to the disease.

POSTER PRESENTATION ABSTRACTS

CLINICAL

THE COGNITIVE EFFECTS OF CEE DEPEND ON WHETHER MENOPAUSE ETIOLOGY IS TRANSITIONAL OR SURGICAL. Acosta JI, Mennenga S, Mayer LP, Braden BB, Bimonte-Nelson HA. Arizona State University; Northern Arizona University; Arizona Alzheimer's Consortium.

Background: The question of whether to take hormone therapy (HT) will impact every woman as she enters reproductive senescence. In women, studies suggest that ovarian hormone loss associated with menopause has deleterious cognitive effects. Results from clinical studies evaluating whether estrogen-containing HT mitigates these effects, and benefits cognition, are discrepant. The type of menopause, surgical or transitional, impacts cognitive outcome in women. The type of menopause that impacts cognitive effects of HT has not been methodically tested in either women or an animal model.

Methods: We used the 4-vinylcyclohexene diepoxide (VCD) rodent model of ovarian follicle-depletion, which mimics transitional menopause, and the traditional rat model of menopause, ovariectomy (OVX), to cognitively test the most commonly-prescribed estrogen therapy in the United States, conjugated equine estrogen (CEE; tradename Premarin).

Results: Here, we show CEE benefited cognition in surgically-menopausal rats, but, in contrast, impaired cognition in transitionally-menopausal rats. Androstenedione, released from the residual transitional menopausal ovary, was positively associated with impaired performance, replicating our previous findings in VCD animals (Acosta et al., 2009).

Conclusion: The current findings are especially salient given that no clinical study testing cognition has methodically separated these two populations of menopausal women for analysis. That we now show surgical versus transitional modes of menopause result in disparate cognitive effects of HT has implications for future research and treatments optimizing HT for menopausal women.

THE EFFECT OF A SLEEP HYGIENE PROGRAM IN REHABILITATION CENTERS WITH ALZHEIMER'S DISEASE PATIENTS. Allen AM, Uiri-Glover JT, Keller C. Arizona State University; Arizona Alzheimer's Consortium.

Background: Alzheimer's disease (AD) accounts for approximately 69.9% of all dementia in the elderly population. Patients with AD often have nocturnally disrupted sleep, including an increase number of nighttime awakenings after falling asleep, increase sleep latency, decrease total sleep time and increased daytime napping. Disruptive sleep, in AD patients, is strongly related to cognitive and functional decline and significantly increases the odds of nursing home placement. The purpose of this proposed study is to develop and evaluate the feasibility of the training of certified nursing assistants (CNA) to implement a Sleep Hygiene program (SHp) for Alzheimer's disease patients in a rehabilitation setting.

Methods: Sleep will be measured by wrist actigraphy and the physical function will be measured by the functional independent measurement (FIM) tool. Design-two group measure of a pretest and post-test design with random assignment of participants to one intervention group or one controlled group to obtain preliminary evidence about the feasibility, safety, and efficacy of an individualized sleep hygiene intervention on sleep and physical function outcome of AD patients. The target audience was patients admitted to a rehabilitation setting. Two rehabilitation facilities will be recruited to participate in this study. The facilities have more than 60 beds and are in a suburban area of Arizona. The facilities were recruited by size, patient population and quality. The population of interest is forty (40) mild to moderate AD patients who were recently admitted to the rehabilitation facilities and CNAs who have had experience working with AD patients. Data will be analyzed using the Wilcoxon Sign nonparametric test to compare the two groups.

Conclusions: Sleep disturbance is common among patients with AD in a rehabilitation setting. The desired outcomes of this study are that AD patients will:

- Increase nighttime sleep
- Decrease daytime sleep
- Increase FIM scores
- Decrease length of stay
- Be trained by CNA

SERVICE BARRIERS AMONG CHINESE AMERICAN ALZHEIMER'S FAMILY CAREGIVERS: SELF-REPORTS VS. PERSPECTIVES FROM PROFESSIONALS. Darden A. Sun F. Arizona State University; Arizona Alzheimer's Consortium.

Background: Patients with Alzheimer's disease (AD) often require intensive care due to declines in their physical, cognitive, and behavioral functioning. As a result, family members who provide care for AD relatives are under great physical burden and emotional strains (e.g., depression, anxiety). Community-based health, mental health, or social services are found to relieve caregiving burden and decrease the depressive symptoms among family caregivers. Yet, caregivers from ethnic minority backgrounds are found to be less likely to benefit from existent service programs due to the variety of service barriers that they face. Although increased research attention has been paid to ethnic minority AD caregivers such as African Americans and Latino Americans, Chinese American AD family caregivers have been infrequently examined. Thus this study aims to shed light on service barriers among Chinese Americans AD family caregivers who live in Phoenix.

Guided by the behavior model (Andersen, 1995) and the practice-oriented model of service use (Yeatts, Crow & Folts, 1992), the researchers consider both caregiver-related and service-related factors to be influential in caregivers' decisions of help-seeking. This study incorporated perspectives from both caregivers and service providers (e.g., physicians, nurses) to gain a thorough understanding of the service barriers faced by Chinese American AD family caregivers.

Methods: To uncover the service barriers from both groups' sides, the researchers conducted two focus group discussions in November and December 2009. In order to allow participants to freely share their experiences, the researchers used least structured open-ended questions in the interviews. The first focus group was comprised of six service professionals who have experience working with Chinese American families. The second focus group consisted of six Chinese American family caregivers who currently provide care or have been provided care for an AD relative in past 12 months. The first group interview was conducted in English while the second group was conducted in Chinese. Both focus group sessions were audio taped and transcribed. The Chinese transcript was translated into English before it was coded. Cross-checking method was used to reach most agreement on coding.

Results: From the service professionals' perspectives, they consider communication barriers, both language and culture-related, a big challenge. Moreover, they speculated that Chinese American families tend to minimize their issues when receiving services from Western healthcare professional because they try to solve the problem within their families. The second focus group considered the lack of knowledge about available services, stigma of the disease, and language barriers to be the major service barriers to service use. Caregivers expressed service needs in following areas: information and skills training relevant to disease stage (e.g., information about the stages of AD, coping skills training, and residential care facility), bilingual and skilled service professionals (e.g., doctors, formal caretakers), and a task force that advocates in supportive services for AD care recipients and their families in the community.

Conclusions: Consistent with the practical model of service use described by Yeatts, Crow and Folts (1992), our findings indicate that barriers in service availability and acceptability are two primary obstacles faced by Chinese American families. Various interventions for dementia families and family caregivers need to be tested and perhaps modified to accommodate the needs of Chinese families. Chinese American family caregivers and patients need to be empowered to understand more about the disease and the health care system through education and skill-building approach.

Poster 41

ALL IN THE FAMILY: LEGAL AND ETHICAL DUTIES FOR INFORMED CONSENT AND DISCLOSURE OF GENETIC RISK INFORMATION TO FAMILIES OF ALZHEIMER'S RESEARCH SUBJECTS. Gulley LM, Marchant GE. Arizona State University; Arizona Alzheimer's Consortium.

A distinguishing characteristic of genetic data that differentiates it from other data collected from research subjects is its familial component. Genetic data not only reveals information about the subject, but also the subject's family. Accordingly, some commentators and precedent suggest that informed consent may need to be obtained from family members before genotyping research subjects. This issue is particularly important in Alzheimer's research because of the well-established genetic association and multigenerational impacts of the condition. This presentation will present the arguments for and against family consent and disclosure in the context of Alzheimer's research. Notwithstanding legitimate arguments on both sides of the debate, we conclude that there should not be an affirmative duty to acquire informed consent from, or disclose results to, family members of research participants. We do argue, however, that research subjects should receive counseling as to the potential implications of their results for their biological relatives, as well as receive instruction on the appropriate steps to take if they wish to share their genetic information with their family members.

STRUCTURED TOTAL LEAST SQUARES FOR VOLUMES OF DISTRIBUTION ESTIMATION IN PET IMAGING. Guo, H, Renaut R, Chen K, Reiman EM. Arizona State University; Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.

Background: The volume distribution (DV), an index for amyloid deposition, is routinely estimated by the Graphical analysis (GA) for PiB (Pittsburgh Compound-B)- Positron Emission Tomography (PET) studies of Alzheimer's disease (AD). We found that the well-known bias of the GA estimated DV is primarily due to model error and noise in the PET data. We recently systematically evaluated the bias associated with the model approximation and developed an alternative to minimize the bias. To further reduce the DV estimation bias, noise effects should also be carefully investigated.

Objective: In this study, we focus on the discussion of DV bias related to noise in the PET scan data, methodology development and its performance evaluation.

Methods: A commonly used method to account of the noise is the simple linear least squares (LLS) which assume the noise is non-correlated and identically distributed. The noise in the GA Logan's equation is actually structured and non-identical. Therefore, we propose to use structured total least squares (STLS) instead of the LLS to estimate DV. Ignoring the model error temporarily in this study, a efficient and effective numerical algorithm was derived for DV estimation. Simulated PiB PET data from AD related brain regions in patients and normal controls to examine the proposed algorithm. 1000 random samples for each of 11 regions of interest (ROI) are tested.

Results: The simulation results show that the proposed method significantly reduces the DV errors from $-15.7\% \pm 4.4\%$ to $-3.9\% \pm 10.5$ as compared with LLS. We also note that STLS is much better than the simple total least squares (TLS) and MA1, which includes huge outliers. Statistical descriptions for three representative ROIs are listed in the attached table while histograms for normalized error (in percentage) for all eleven ROIs and four methods, LGA, MA1, TLS and STLS are presented in the attached figure.

Conclusions: We conclude that the proposed STLS method is appropriate for DV estimation in AD PiB PET studies. Additional studied are under-going to incorporate procedures for bias correction related to model error and noise structure.

MINING ADVERSE REACTIONS IN USER POSTS TO HEALTH-RELATED WEBSITES.

Leaman R, Wojtulewicz L, Sullivan R, Skariah A, Yang J, Gonzalez G. Arizona State University; Arizona Alzheimer's Consortium.

Background: Adverse drug reactions (ADRs) are both a common cause of death and carry a significant economic cost. Clinical trials do not find all ADRs, and post-marketing surveillance (pharmacovigilance) relies primarily on voluntary reporting by medical professionals, causing their frequency to be under-reported. Data reported by the patients themselves has become an increasingly important resource, however, with efforts such as MedWatch from the FDA allowing ADR reports directly from the consumer.

Methods: We evaluate automatically mining the relationships between drugs and adverse reactions as reported by the patients themselves in user comments to health-related websites. We utilize a lexical approach with terms from the UMLS Metathesaurus, the MedEffect database, and the SIDER side effect resource. We additionally use approximate string matching to handle the large number of spelling errors in the user comments.

Results: We evaluate our system on a 3,600 manually-annotated user comments from 4 different drugs, achieving a promising precision of 59.8%, a recall of 70.5% and an f-measure of 64.6%. We also compared the frequency of adverse drug reactions found by our system in unlabeled data with the frequency of known adverse drug reactions, noting strong correlations for the common reactions.

Conclusions: We conclude that user comments pose a significant natural language processing challenge, however they do contain useful extractable information which merits further exploration.

UNCOVERING NOVEL GENES IN ALZHEIMER'S DISEASE: SENSITIVITY COMPARISON OF DATA SOURCES. Lee J, Gonzalez G. Arizona State University; Arizona Alzheimer's Consortium.

Background: A gene expression data set comprising of control and AD samples was used in order to analyze potential genes relevant in AD etiology and pathology. Even though expression data has relatively high noise levels, suitable statistical processing enables extraction of information that could enable the and prioritization of potentially novel gene targets relevant to Alzheimer's disease development.

Methods: Gene expression data from the Gene Expression Omnibus (accession number GSE15222) comprising 187 normal and 68 AD samples interrogating 16400 genes was obtained, and differential expression levels of genes were analyzed by applying Wilcoxon ranked test. Observations from the gene expression dataset were compared to GWAS and protein interaction data.

Results: Wilcox ranked test revealed 66 genes were significantly differentially expressed with P-values < 0.05 (Set_sig). Transcription factors are over-represented in the set possibly indicating a large number of gene regulation pathways are quantitatively altered in AD cells as compared to normal cells. Genes in cell-cycle and apoptosis pathways are also over-represented. In terms of cellular location, many gene products were located on cellular membrane. Large number of pathways were represented by the genes possibly implying AD is a phenotype at whole cell scale and large number of pathways are affected. A number of genes that have been previously established to be of high relevance to AD through GWAS study were pinpointed in the dataset (APOE, APP, PSEN1, PSEN2 of strong susceptibility and CLU, PICALM and CR1 of smaller odds ratio values). The APOE gene showed nearly identical expression levels (P-value=0.3453) across normal and AD samples which is consistent with the known mechanism of resistance to clearance that is the main factor in late onset AD development due to APOE, instead of its altered expression level. PSEN1, PSEN2 and CLU showed moderate degrees of altered expression levels with respective P-values 0.0243, 0.0141 and 0.0122. The CR1 gene was significantly up-regulated in AD samples (P-value=5.2e-9). There were 20 proteins corresponding to Set_sig genes without known interacting proteins and 16 proteins that only report between 1 and 5 interacting proteins. A large number of protein interactions of the set's proteins were involved in ribosome assembly.

Conclusions: Many genes showing significant differential expression levels were new and have not been identified through previous studies such as GWAS. Hence GWAS was seen to have sensitivity towards detection of certain AD genes which are fairly distinct from those detected through expression analysis. Conversely, genes identified through differential expression analysis can serve as interesting lead genes in investigation of AD. Relatively under-identified number of protein interactants in the set implies genes which would have been missed through protein interaction study can be cast due light in an expression study. Overall, expression, GWAS and protein interaction each have its own sensitivity towards detection of genes. Work on a gene prioritization approach that maximizes the utility of heterogeneous data sources in a complementary manner would be ideal for uncovering potentially new targets for AD pathology elucidation and therapeutic interventions.

IMMUNOSIGNATURE OF ALZHEIMER'S DISEASE. Restrepo L, Stafford P, Magee DM, Johnston SA. Arizona State University; Arizona Alzheimer's Consortium.

Background: A challenge in Alzheimer's disease (AD) research is that there are no specific diagnostic tests for this type of dementia. Diagnosis is based on exclusion of other conditions, rather than testing directly for AD; since this misdiagnoses 1/5 patients, reliable laboratory tests are needed. The recent finding that AD patients have alterations in humoral immune response, including anti-beta amyloid (A β) antibodies, opens new opportunities for testing the merits of immunoassays. We describe herein a proteomic platform to assist in the differentiation between dementia and normal senescence, called "immunosignature."

Methods: The platform consists of a customized microarray with 10,000 random-sequence 17mer peptides printed on a glass slide, which is probed with an antibody of interest. Antibodies binding to the array are subsequently detected with species-specific biotinylated antibodies, followed by streptavidin-Alexa555. This detects antibody binding patterns, allowing identification of peptides mimicking actual epitopes targeted by donor's serum. We purchased 11 affinity-purified antibodies: 7 against A β (4 monoclonal, 3 polyclonal) and 3 against tau (2 monoclonal, 1 polyclonal). A polyclonal antibody against human albumin was also included. Serum samples from 15-month old *APP^{swe}/PSEN1-IdE9* transgenic mice (n=5) and non-transgenic mice (n=4) were assayed, as well as sera from 12 demented patients (11 with AD, 1 with progressive supranuclear palsy, PSP) and 12 normal elderly non-demented controls (NDC).

Results: Each individual affinity-purified antibody showed distinct binding pattern on the array. The microarray discriminated between mice groups on heat maps and principal component analysis (PCA). Human plasma was pooled as follows: (1) Autopsy-proven AD (n=4), (2) AD without autopsy (n=7), (3) NDC without AD pathology on autopsy (n=4), (4) NDC without autopsy (n=8), and (4) PSP sera. PCA showed distinctive segregation of AD immunosignature from the NDC pools, whereas PSP sera migrated in between. Using a training set, 8 blinded individual samples were assayed and assigned to either AD or NDC; the technique correctly recognized 4 AD and 2 control cases, but misclassified 2 samples (1 erroneously assigned to AD group, the other to NDC).

Conclusions: Here we show preliminary results with a simple and reliable test to assess humoral immunity repertoire of AD and NDC. We are currently testing a larger cohort of patients and NDC to determine sensitivity and specificity of this technology.

ALZHEIMER BIOMEDICAL DATA WAREHOUSE USING I2B2 PLATFORM. Yang J, Sullivan R, Mukund K, Wilkinson W, Skariah A, Gonzalez G. Arizona State University; Arizona Alzheimer's Consortium.

Background: Informatics for integrating Biology and the Bedside (i2b2) is an NIH-funded initiative based at Harvard University and Partners HealthCare system in Boston Mass. It was designed to create a comprehensive software system with tools and methodological frameworks that can be disseminated at no extra cost to the user, as open source product, to enable clinical researchers to accelerate the translation of genomic and traditional clinical findings into novel diagnostics, prognostics and therapeutics.

The National Alzheimer's Coordinating Center (NACC) was established by the National Institute on Aging to facilitate collaborative research among the 29 NIA-funded Alzheimer's Disease Centers (ADCs) nationwide. NACC developed and maintains a large relational database of standardized clinical and neuropathological research data collected from each ADC which is valuable resource for both exploratory and explanatory Alzheimer's disease research.

Methods: This project uses the data from the Arizona ADC and is referred to as ADCC data hence forth. The goal of our project in keeping with the aim of i2b2 is to integrate the ADCC data into i2b2 to enable clinical researchers to accelerate the translation of genomic and traditional clinical findings into novel diagnostics, prognostics and therapeutics. The first step toward integration requires the modification of the transactional data model of the ADCC data base into a star data warehouse model, which can then be migrated into i2b2. After data is loaded into the data warehouse model through ETL process, custom plug in on top of i2b2 can be developed. Ontology hierarchy is also developed within i2b2.

Results: This project was undertaken with an effort to integrate Alzheimer's data into the i2b2 framework to provide researchers with ability to easily access and query such data. The current data warehouse contains data dates back to 2003, and has different schemas (UDS-compliant for newer visits, legacy data in an Arizona-specific format). Content available for researchers includes demographics, diagnoses, Laboratory tests, medications and procedures. On top of the data warehouse, the following tools are available as well:

1. Automated tools for cohort identification and hypothesis generation.
2. Creation of Alzheimer data warehouse for later statistical analysis.
3. Adopt Natural language processing for unstructured data.
4. Custom reporting and analysis tools for Alzheimer data.

Conclusions: With ADCC data successfully integrated into i2b2 platform, there will be great benefit for research on Alzheimer, researchers can pull from i2b2 to augment research data or push research data into i2b2, and easier access to new information can be provided.

TWELVE-MONTH WHOLE-BRAIN ATROPHY RATES AND ESTIMATED POWER TO DETECT ALZHEIMER'S DISEASE-SLOWING TREATMENT EFFECTS IN MULTI-CENTER TRIALS USING ITERATIVE PRINCIPAL COMPONENT ANALYSIS: PRELIMINARY FINDINGS FROM THE ALZHEIMER'S DISEASE NEUROIMAGING INITIATIVE. Ayutyanont N, Chen K, Reschke C, Langbaum JBS, Fleisher A, Kong L, Liu X, Lee W, Huan Z, Reiman EM. Arizona Alzheimer's Institute; Banner Good Samaritan Medical Center; Arizona State University; Beijing Normal University; University of Arizona; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Background: Like the extensively used Brain-Boundary Shift Integral, the Iterative Principal Component Analysis (IPCA) can be used to characterize differential rates of whole-brain atrophy from sequential volumetric magnetic resonance images (MRIs) in probable Alzheimer's disease (AD) patients and normal controls (Chen et al, 2004) and in cognitively normal people at three levels of genetic risk for late-onset AD (Chen et al, 2007).

Objective: To automatically characterize twelve-month whole-brain atrophy rates in 147 probable AD patients, mild-cognitive impairment (MCI) patients, and elderly normal controls (NCs) from the AD Neuroimaging Initiative using IPCA and estimate the respective number of probable AD and MCI patients needed per group to detect AD-slowing treatment effects in twelve-month multi-center randomized clinical trials (RCTs).

Methods: The IPCA was used to characterize twelve-month whole-brain atrophy rates in 34 mildly affected probable AD patients, 75 amnesic MCI patients, and 38 elderly NCs. Whole-brain atrophy rates and clinical and cognitive ratings were subsequently used for sample size estimates.

Results: The IPCA detected significantly different twelve-month whole brain atrophy rates in the probable AD, MCI and NC groups, which were associated with categorical measures of clinical disease severity (AD>MCI>NC): $0.60\pm 0.23 > 0.37\pm 0.28 > 0.28\pm 0.24$ percent, respectively (ANOVA $p=1e-6$, linear trend $p=7e-7$). We estimate the need for 47 probable AD patients per treatment arm to detect a 25% disease-slowing effect in a twelve-month multi-center RCT using IPCA-characterized whole-brain atrophy rates $p=0.05$ and 80% power method. Using various clinical and cognitive ratings such as CDR-SB, ADAS-Cog and MMSE, 376, 468 and 809 probable AD patients are needed, respectively. Similarly, we estimate the need for 147 MCI patients per arm to detect a 25% disease-slowing effect in a twelve-month multi-center RCT, compared with 744, 1975 and 1896 MCI subjects needed, respectively, using CDR-SB, ADAS-Cog and MMSE.

Conclusion: Results from these initial ADNI analyses suggest the promise of using the IPCA to automatically characterize whole-brain atrophy rates in the evaluation of putative AD-slowing treatments.

USE OF AN ALZHEIMER'S DISEASE-RELATED HYPOMETABOLIC CONVERGENCE INDEX TO PREDICT PROGRESSION FROM MILD COGNITIVE IMPAIRMENT TO ALZHEIMER'S DEMENTIA. Chen K, Ayutyanont N, Langbaum JBS, Fleisher A, Reschke C, Lee W, Ziaofen L, Alexander GE, Bandy D, Foster NL, Weiner MW, Koeppe RA, Thompson PM, Jagust WJ, Reiman EM, Alzheimer's Disease Neuroimaging Initiative. Banner Alzheimer's Institute; Banner Good Samaritan Medical Center; Arizona State University; Evelyn F. McKnight Brain Institute; University of Arizona; University of Utah, University of California, San Francisco; University of Michigan; University of California, Berkeley; Translational Genomics Research Institute; University of California, Los Angeles; Arizona Alzheimer's Consortium.

Background: Using fluorodeoxyglucose positron emission tomography (FDG PET) data from the Alzheimer's Disease Neuroimaging Initiative (ADNI), we introduce the concept of an AD-related "hypometabolic convergence index (HCI)," a single voxel-based index which, in comparison with data from normal control (NCs), reflects the extent to which the pattern and magnitude of hypometabolism in an individual subject converges with the pattern and magnitude of hypometabolism in probable AD patients.

Objective: To characterize and compare the ability of HCIs, other magnetic resonance imaging (MRI) and cerebrospinal fluid (CSF) measurements, memory scores and clinical ratings in predicting 18-month progression from mild cognitive impairment (MCI) to Alzheimer's dementia.

Methods: After using a cross-validation procedure to identify the threshold for each biomarker, cognitive, or clinical measurement to distinguish between MCI converters and non-converters, the Cox proportional hazards model was used to characterize and compare the prediction ability of "abnormal" HCIs, hippocampal volumes, CSF $A\beta_{1-42}$, t-tau, p-tau_{181p} levels and ratios, auditory verbal learning test total and long-term memory (LTM) scores, and three different clinical ratings to predict time-to-progress to Alzheimer's dementia.

Results: Abnormally high HCI's and small hippocampal volumes were associated with the highest odds of 18-month progression from MCI to Alzheimer's dementia (OR=7.38 and 6.35, respectively), more likely to progress to AD than those who were normal. ORs for the other biomarker, cognitive and clinical measurements were between 1.33 and 4.94. MCI patients with both an abnormally high HCI and abnormally small hippocampal volume had an even higher odds ratio of clinical progression (OR=36.72), and each of these measurements were correlated with cognitive and clinical measurements of disease severity in the overall group of probable AD, MCI and NC subjects.

Conclusion: While additional studies are needed, the HCI offers promise in automatically characterizing the AD-related pattern of hypometabolism in FDG PET images in a single measurement, predicting progression from MCI to Alzheimer's dementia alone or in combination with hippocampal volume measurements, and providing an indicator of disease severity in different clinical and research settings. Among other things, it raises the possibility of generating Alzheimer's disease-related convergence indices using imaging modalities and voxel-based data analysis algorithms.

ASSOCIATION BETWEEN AN ALZHEIMER'S DISEASE-RELATED HYPOMETABOLIC CONVERGENCE INDEX IN COGNITIVELY NORMAL LATE-MIDDLE-AGED PEOPLE AND THREE LEVELS OF GENETIC RISK FOR LATE-ONSET ALZHEIMER'S DISEASE.

Fleisher A, Chen K, Ayutyanont N, Auttawut R, Langbaum JBS, Lee W, Liu X, Bandy D, Reeder SQ, Alexander GE, Caselli RJ, Reiman EM, Alzheimer's Disease Neuroimaging Initiative. Banner Alzheimer's Institute; Banner Good Samaritan Medical Center; Arizona State University; University of Arizona; University of California, San Diego; Mayo Clinic Arizona; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Background: Using fluorodeoxyglucose positron emission tomography (FDG PET) data from the Alzheimer's Disease Neuroimaging Initiative (ADNI), we recently introduced the concept of an AD-related "hypometabolic convergence index"(HCI). We demonstrated its potential to predict progression to probable AD in patients with mild cognitive impairment (MCI). The HCI is a voxel-based summary score that reflects the extent to which the pattern and magnitude of hypometabolism in an individual's PET image converges with the pattern and magnitude of hypometabolism in a group of probable AD patients.

Objective: To characterize the association between *apolipoprotein E (APOE) ε4* gene dose and the AD-related HCI in late-middle-aged cognitively normal $\epsilon 4$ homozygotes (HM), heterozygotes (HT), and non-carriers (NC) from our ongoing longitudinal study.

Methods: Using SPM5, FDG PET scans from 68 participants with AD were compared to 78 elderly healthy controls from the ADNI dataset to establish a regional-to-whole brain z-score map of AD-like hypometabolism. From a separate cohort of 160 cognitively normal individuals age 47-68 (56.68 ± 4.64), including 78 NC, 46 HT, and 36 HM, FDG PET images were compared to the same ADNI healthy control dataset to create comparative hypometabolic maps of each individual subject. HCI, the consistency between the individual hypometabolism maps and the AD-like map, was calculated as the sum of the product of z-scores from each cerebral voxel from these two maps. HCI scores were compared between NC, HT and HM groups.

Results: While the HM, HT, and NC groups did not differ significantly in their age, gender, educational level, or neuropsychological test scores, the three groups differed significantly in their HCI's (24.38 ± 4.84 , 23.58 ± 3.59 , and 21.80 ± 4.09 , respectively; ANOVA, $p=0.004$). Additionally, there was a significant association between HCI's and *APOE ε4* gene dose (linear trend, $p=0.001$).

Conclusion: The AD-related HCI in cognitively normal late-middle-aged people is associated with three levels of genetic risk for late-onset AD. This index score offers promise in the pre-symptomatic detection and tracking of AD-associated hypometabolism, assessment of genetic and non-genetic risk factors, and evaluation of promising AD-modifying treatments in pre-symptomatic individuals.

ASSOCIATION BETWEEN CEREBRAL PATTERNS OF FIBRILLAR AMYLOID-BETA BURDEN AND GLUCOSE HYPOMETABOLISM IN COGNITIVELY NORMAL OLDER ADULTS AT THREE LEVELS OF GENETIC RISK FOR LATE-ONSET ALZHEIMER'S DISEASE. Fleisher A, Chen K, Liu X, Ayutyanont N, Langbaum JBS, Lee W, Reeder SA, Alexander GE, Bandy D, Caselli RJ, Reiman EM. Banner Alzheimer's Institute; Banner Good Samaritan Medical Center; Arizona State University; University of Arizona; University of California, San Diego; Translational Genomics Research Institute; Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

Background: We previously found that *apolipoprotein E (APOE) ε4* gene dose, reflecting three levels of genetic risk for late-onset Alzheimer's disease (AD), is associated with characteristic patterns of glucose hypometabolism and fibrillar amyloid-beta ($A\beta$) burden in cognitively normal older adults (Reiman et al, 2004; 2009). We have also introduced an automated algorithm, known as multi-modal partial least squares (MMPLS), to characterize the linkage between patterns in two or more complementary complex data sets from the same person on a voxel-by-voxel basis (Chen et al, 2009).

Objective: To use MMPLS to characterize how *APOE ε4* gene dose is associated with patterns of cerebral hypometabolism and fibrillar $A\beta$ burden. To investigate how metabolic and $A\beta$ measurements, in respective clusters of preferentially affected voxels, are related to each other.

Methods: MMPLS was used in "informed mode" for the simultaneous analysis of fluorodeoxyglucose (FDG) and Pittsburgh Compound B (PiB) positron emission tomography (PET) images from 11 $\epsilon 4$ homozygotes, 11 $\epsilon 4$ heterozygotes, and 16 $\epsilon 4$ noncarriers who were cognitive normal (65 ± 5 years old). Patterns of cerebral-to-whole brain FDG PET counts and cerebral-to-cerebellar PiB Distribution Volume Ratios (DVRs) most closely associated with *APOE ε4* gene dose were characterized.

Results: $\epsilon 4$ homozygote, heterozygote, and non-carrier groups did not differ significantly in their age, gender distribution, educational level, Mini-Mental State Examination (MMSE) scores (29.6 ± 0.8), or Auditory Verbal Learning Test (AVLT) long-term memory scores. Patterns most closely associated with *APOE ε4* gene dose were notable for lower glucose metabolism in the precuneus and posterior cingulate cortex and increased fibrillar $A\beta$ in the precuneus, posterior cingulate cortex and medial prefrontal cortex. As expected, there was a strong correlation between lower cerebral glucose metabolism and higher fibrillar $A\beta$ in respective empirically defined statistical regions-of-interest (comprised of voxels associated with $\epsilon 4$ gene dose at $p\leq 0.005$) in all 38 subjects ($r=-0.46$, $p=0.0039$) and in the 22 $\epsilon 4$ carriers ($r=-0.47$, $p=0.028$). Larger sample sizes are needed to further characterize the relationships for each *APOE* genotype.

Conclusion: There is a strong relationship between the pattern of regional hypometabolism and fibrillar $A\beta$ deposition associated with three levels of genetic risk for late-onset AD in cognitively normal adults.

NEUROIMAGING BIOMARKERS TRACK BRAIN DEGENERATION IN 676 SUBJECTS WITH ALZHEIMER'S DISEASE, MILD COGNITIVE IMPAIRMENT, AND HEALTHY CONTROLS. Hua X, Lee S, Leo AD, Yanovsky I, Parikshak N, Chou Y-Y, Ho AJ, Gutman B, Toga AW, Jack Jr. CR, Bernstein MA, Reiman EM, Harvey DJ, Kornak J, Schuff N, Alexander GE, Weiner MW, Thompson PM, Alzheimer's Disease Neuroimaging Initiative. University of California, Los Angeles; California Institute of Technology; Mayo Clinic Rochester; Banner Alzheimer's Institute; University of Arizona; University of California, Davis; University of California, San Francisco; University of Arizona; Arizona Alzheimer's Consortium.

Background: Alzheimer's disease (AD) is a devastating brain disorder that causes enormous personal, social and economic burden; it affects more than 5 million elderly people in the U.S., and over 24 million worldwide. Magnetic resonance imaging (MRI) can measure disease progression, and shows promise for assessing new therapeutic agents and treatment efficacy in clinical trials.

Methods: In one of the largest MRI studies to date, we used tensor-based morphometry (TBM) to create 3D maps of structural brain atrophy in 676 subjects with AD (N=165; age: 75.6 ± 7.6 SD years), mild cognitive impairment (MCI; N=330; 74.8 ± 7.5), and healthy elderly controls (N=181; 75.9 ± 5.1), as part of the Alzheimer's Disease Neuroimaging Initiative (ADNI). Baseline temporal lobe atrophy was correlated with current cognitive performance, future cognitive decline, and conversion from MCI to AD over the following year; it predicted future decline even in healthy subjects. Over half of the AD and MCI subjects carried the ApoE4 allele, a known risk gene for AD, and they showed greater hippocampal and temporal lobe deficits than age-, gender- and diagnosis-matched non-carriers. ApoE2 gene carriers, around 1/6 of the normal group, showed reduced ventricular expansion versus non-carriers, suggesting a protective effect even in healthy controls.

In one-year follow-up scans from the same subjects, rates of brain atrophy were correlated with interval changes in the sum-of-boxes clinical dementia rating (CDR-SB), mini-mental state examination (MMSE), and logical memory test scores. Temporal lobe atrophic rates correlated very highly with CSF Tau/Abeta ratio, less so with Abeta(1-42), Tau, pTau/Abeta, pTau in that order; in AD, atrophic rates correlated with pTau and Tau more than Abeta.

Results: Using TBM-derived measures of temporal atrophy, in a statistically pre-defined region of interest within the temporal lobe, only 48 AD and 88 MCI subjects were needed to provide 80% power to detect a 25% reduction in the mean annual rate of change ($\beta=0.05$; 2-tailed test). This is a drastic sample size reduction relative to using clinical scores as outcome measures (619 AD/6797 MCI for the ADAS-Cog, and 408 AD/796 MCI for the CDR-SB).

Conclusion: As a potential outcome measure, TBM provides high statistical power to track clinically meaningful brain changes, and may save time and costs for large, multi-site neuroimaging studies and clinical trials in AD.

ASSOCIATION BETWEEN PULSE PRESSURE AND FIBRILLAR AMYLOID-BETA BURDEN IN COGNITIVELY NORMAL LATE-MIDDLE-AGED PEOPLE AT THREE LEVELS OF GENETIC RISK FOR ALZHEIMER'S DISEASE. Langbaum JBS, Chen K, Liu X, Fleisher AS, Reeder SA, Bandy D, Alexander GE, Caselli RJ, Reiman EM. Banner Alzheimer's Institute; Banner Good Samaritan Medical Center; Arizona State University; University of California, San Diego; University of Arizona; Mayo Clinic Arizona; Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Background: Epidemiological studies suggest an association between cardiovascular disease risk factors in mid-life and Alzheimer's disease (AD) in late-life. In the present study we used Pittsburgh Compound-B (PiB) positron emission tomography (PET) to examine the relationship between blood pressure (BP) measures and this brain imaging measurement of presymptomatic AD in a cohort of cognitively normal, late middle-aged *APOE* ϵ 4 homozygotes (HM), heterozygotes (HT) and noncarriers (NC).

Methods: Mean systolic and diastolic BP was computed from three supine measurements. SPM5 was used to characterize relationships between systolic BP (SBP), diastolic BP (DBP) and peripheral pulse pressure (PP) with regional-to-cerebellar PiB PET distribution volume ratios (DVR) in 32 cognitively normal persons (mean age 65.5 ± 4.5), including 8 HM, 11 HT, and 13 NC.

Results: The *APOE* ϵ 4 groups did not differ significantly in demographic characteristics, clinical ratings or neuropsychological test scores. 19% of the participants' BP measurements met criteria for hypertension and 34% reported using antihypertensive medications. SBP was positively correlated and DBP negatively correlated with PiB DVR bilaterally in frontal, temporal and precuneus regions ($p < 0.005-0.05$ uncorrected). Higher PP was associated with increased PiB DVR bilaterally in frontal and posterior cingulate-precuneus regions ($p < 0.005-0.05$, uncorrected). Controlling for *APOE* ϵ 4 did not significantly alter these findings. The PP PiB DVR correlations were significantly greater than the SBP or DBP correlations. Restricting the PP analysis to only normotensive individuals who did not report using antihypertensive medications, higher PP was associated with increased PiB DVR bilaterally in frontal, posterior cingulate, precuneus and medial temporal brain regions ($p < 0.005-0.05$, uncorrected), with no correlations in the opposite direction.

Conclusions: These findings provide additional evidence that increases in pulse pressure in mid-life may be associated with increased risk of AD pathology. This study provides a rationale for using brain imaging to rapidly evaluate the efficacy of antihypertensive medications for the presymptomatic treatment of AD.

PREDICTION OF BEHAVIORAL SCORES BASED ON HEMISPHERIC CORTICAL SURFACE MAPS OF FDDNP. Protas H, Huang S-C, Kepe V, Ercoli L, Thompson P, Small GW, Barrio J. University of California, Los Angeles; Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.

Background: Alzheimer's disease (AD) is characterized by the presence of beta amyloid plaque and neurofibrillary tangles in various brain regions. 2-(1-{6-[(2-[F- 18]fluoroethyl)(methyl)amino]-2-naphthyl}ethylidene)malononitrile ([F-18]FDDNP) is one of the recently introduced PET tracers that enable the detection of beta amyloid and neurofibrillary tangles in living patients.

Objective: Hemispheric Cortical Surface Maps (HCSM) of FDDNP give good visualization of beta amyloid plaque (BA) and neurofibrillary tangle (NFT) distribution in the brain. To quantify the distribution pattern in terms of behavior deterioration, we examined the feasibility and reliability of using an estimation method to predict a subject's MMSE based on his regional cortical FDDNP uptake pattern.

Methods: Movement correction is applied to dynamic FDDNP PET from 23 subjects that have Mini Mental State Examination (MMSE) scores. Logan graphical plots were used, with cerebellum as reference region, to generate the DVR image of FDDNP. Early summed FDDNP images were calculated. A HCSM for each subject was extracted from the MRI in ICBM space. The same transformations were applied to the DVR and summed FDDNP images to put them in the same cortical space. ROIs were drawn directly on the average HCSM. Linear regression was used to find the rate of change of FDDNP vs MMSE for each ROI on the cortical surface. The models were then used jointly to estimate MMSE from a set of ROI values of a subject. Cross validation was used to show the reliability of the estimate.

Results: Use of all ROI values of DVR to estimate MMSE gave a sample standard deviation (SD) of 2.3 that was comparable to value of using the global DVR alone. With stepwise approach, we found that the SD can be reduced to 1.7 by using only DVR values from prefrontal, medial temporal, lateral temporal, parietal regions plus the early summed FDDNP value in posterior cingulate.

Conclusion: HCSM of FDDNP can provide not only good visualization of brain cortical distribution of BA and NFT, but also reliable estimates of subject's MMSE, when proper statistical estimation is employed.

IS THERE AN INCREASED RISK OF DEATH FROM NATURAL CAUSES IN YOUNG ADULT APOLIPOPROTEIN E E4 CARRIERS? Yaari R, Langbaum JBS, Corneveaux JJ, Huentelman MJ, Beach TG, Roher A, Valla J, Caselli RJ, Reiman EM. Banner Alzheimer's Institute; Translational Genomics Research Institute; Banner Sun Health Research Institute; Barrow Neurological Institute, Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

Objective: Besides its association with Alzheimer's disease (AD), the *apolipoprotein E (APOE) ε4* allele may be associated with a higher risk of cardiovascular disease, parasitic, bacterial, and viral infections, hastened progression of AIDS and multiple sclerosis, worse outcome after traumatic brain injury, and shorter lifespan. Here we raise the possibility of an association between the *APOE ε4* allele and a higher risk of death in young adults.

Methods: The proportion of *APOE ε4* carriers was characterized in a discovery cohort of 60 brain donors and a replication cohort of 80 brain donors from the Maryland Brain Bank who were 18-40 years (28±7) years old and whose deaths were not attributed to neurological causes.

Results: In the discovery cohort, *APOE ε4* carriers accounted for 38% of brain donors, including 61% whose deaths were attributable to natural causes—significantly greater than the 24% of *ε4* carriers in an historical control group of living adults (two-tailed χ^2 , $p=0.04$ and $p=0.002$, respectively). In the replication cohort, *APOE ε4* carriers accounted for 25% of brain donors, including 35% whose deaths were attributable to natural causes—greater than the expected distribution of *ε4* carriers in the historical control group, but not significantly so ($p=0.79$ and $p=0.41$, respectively). While young adult *APOE ε4* carriers had greater odds of death from natural causes than *ε4* non-carriers (unadjusted logistic regression, OR=2.6 [95%CI=1.2-5.4], $p=0.01$ in the combined group), this difference did not remain significant after adjustment for age (31±7 versus 26±7 years) and race (47% Black and 53% White versus 27% Black and 73% White), (OR=0.99 [95%CI=0.4-2.6], $p=1.0$).

Conclusions: Additional studies are needed to address the possibility that young-adult *APOE ε4* carriers have an increased risk of death from natural causes, control for potential confounds and, if substantiated, clarify the biological basis for this risk.

HIPPOCAMPAL GRAY MATTER VOLUME DECLINES AT A FASTER RATE IN COGNITIVELY NORMAL APOE E4 CARRIERS Baxter LC, Liu S, Chen K, Caselli RJ. Barrow Neurological Institute; Banner Alzheimer's Institute; Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

Objective: To compare voxel-based morphometry (VBM) measurements of gray matter integrity in cognitively normal carriers and non-carriers of the apolipoprotein (APOE) e4 allele, a common Alzheimer's disease (AD) susceptibility gene.

Background: APOE e4 is a major risk factor for Alzheimer's disease. Even in the absence of symptomatic impairment, memory declines in e4 carriers on the Auditory Verbal Memory Test (AVLT) Long Term Memory score (LTM) prior to age 60 years (Caselli et al., 2009).

Methods: All subjects were participants in a Mayo Clinic Arizona longitudinal APOE study and were all cognitively normal. High resolution T1 SPGR scans were obtained on a 3 Tesla GE scanner at the Barrow Neurological Institute. Age range was similar between groups (Carriers: n=35; 35-85 yrs; Noncarriers: n= 35; 32-87 yrs). SPM5 was used to perform automated whole brain group VBM analyses of gray and white matter, showing anterior and posterior hippocampal regions of significant decline with age. Region of interest (ROI) analyses were done on significant hippocampal regions to determine the age by APOE interaction.

Results: Significant age-related changes were observed, including the anterior (coordinates: -29,-9,-21) and posterior (-26,-37,-3) left hippocampus. Comparing slopes of decline between APOE e4 carriers and noncarriers showed a greater decline in carriers in the posterior hippocampus (p=0.01) and a similar but non-significant difference in the anterior hippocampus (p=0.16). Both regions appear to show a decline in carriers that occurs prior to 60 years, with little decline observed in the noncarriers.

Conclusions: Consistent with the verbal memory decline, APOE e4 carriers who are cognitively intact show declines in gray matter volume in the hippocampus, a region critical for memory function. This decline occurred in adults prior to the age of 60 while hippocampal gray matter decline was minimal among noncarriers.

THE COGNITIVE RESERVE REFLECTED IN SEX DIFFERENCES IS NOT ALTERED BY APOE GENOTYPE. Baxter LC, Dassel K, Dueck A, Caselli RJ. Barrow Neurological Institute; Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

Objective: To determine whether sex-related superior cognitive skills are altered by age-related declines in APOE e4 carriers.

Background: APOE e4 is a major risk factor for Alzheimer's disease. Even in intact adults, memory declines in e4 carriers on the Auditory Verbal Memory Test Long Term score (AVLT-LTM) prior to age 60 years, and spatial performance on Judgment of Line Orientation (JLO) after age 60 years (Caselli et al, 2009). Women outperform men on some tests, including verbal memory, while men perform better on visuospatial tests.

Design/Methods: Cognitively normal participants, aged 21-97, grouped by APOE e4 genotype, were assessed every one to two years. We estimated the longitudinal effect of age using statistical models simultaneously modeling cross sectional and longitudinal effects on AVLT-LTM and JLO using quadratic models to determine the effects of sex, APOE e4, and their interaction.

Results: 253 men (154 noncarriers/99 carriers) were slightly older (mean age = 53.5 vs. 51.5 years; $p = 0.015$) and more educated (16.1 vs. 15.1 years; $p < 0.001$) than 562 women (344 noncarriers/218 carriers). On the AVLT women performed better at all ages ($p < 0.01$). APOE e4 carriers performed worse than noncarriers with no significant interaction. Across all ages, men performed better on the JLO ($p < 0.001$), with no APOE effect. There were no differences in rate of decline on either test between men and women, though performance of the superior group remained better than that of the inferior group throughout follow-up.

Conclusions: Sex and APOE e4 both influenced cognitive decline but did not interact. Both sexes showed decreased performance with age regardless of their superiority on a given task. Our findings suggest that 1) evidence of cognitive reserve depends on the task measured and 2) the appearance of preserved cognitive reserve on a given task does not result in protection against decline.

ARE ALZHEIMER'S PATIENTS HEALTHIER? A CLINICOPATHOLOGICAL STUDY.
Beach TG, Maarouf CL, Brooks RC, Shirohi SW, Daugis ID, Sue LI, Vedders LJ, Lue LF, Walker DG, Sabbagh MN, Roher AE. Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

Background: This question was the title of an article published in 1988 (Wolf-Klein et al). Subsequently there have been several similar articles (see references below), all suggesting that subjects with Alzheimer's disease (AD) have fewer diagnosed medical conditions than age-similar cognitively normal subjects. Two major explanatory hypotheses have been offered: 1) Medical conditions are under-detected and/or under-reported in subjects with dementia 2) Subjects with dementia are healthier. There would be important implications for AD and dementia care and research if either of these were true. Previous studies have been limited by not having autopsy confirmation of diagnosed conditions.

Methods: Private medical records review of 323 neuropathologically-confirmed AD cases, 70 subjects with non-Alzheimer's dementias (NADD), and 122 non-demented subjects was supplemented by a sub-study in which medical records reports of cardiovascular conditions were compared with autopsy measures of heart pathology in 35 subjects with AD and 22 non-demented controls.

Results: Subjects with AD and NADD had significantly fewer total health conditions reported than controls; 11.9, 13.0 and 17.3 per subject, respectively. Conditions that were significantly less common in the dementia groups were hypertension, coronary artery disease, congestive heart failure, osteoporosis, arthritis, and cataracts. In the cardiovascular sub-study, AD subjects had significantly fewer clinically-diagnosed cardiovascular conditions (2.85 vs 4.18), decreased coronary artery stenosis (71.8% vs 76.3%), heart weight (402 vs 489 g for males; 319 vs 412 g for females) and valvular circumferences, with all of these differences being more marked in females. Carriage of the Apolipoprotein E-ε4 allele did not influence the degree of coronary artery stenosis. Body Mass Index (BMI) was significantly greater in the control group and the BMI difference between AD and controls was greater amongst females.

Conclusions: Private physicians diagnose fewer conditions in elderly subjects with dementia as compared to non-demented age-similar subjects. Possible explanations for this finding include better metabolic and cardiovascular health in dementia due to decreased caloric intake, and under-detection and/or under-reporting of associated medical conditions in demented subjects. A wider implication is that weight loss is beneficial to cardiovascular health even at advanced age.

MULTI-ORGAN DISTRIBUTION OF PHOSPHORYLATED ALPHA-SYNUCLEIN HISTOPATHOLOGY IN SUBJECTS WITH LEWY BODY DISORDERS. Beach TG, Adler CH, Sue LI, Vedders L, Lue LF, White CL, Akiyama H, Caviness JN, Shill HA, Sabbagh MN, Walker DG. Banner Sun Health Research Institute; Mayo Clinic Arizona; University of Texas Southwestern Medical Center; Tokyo Institute of Psychiatry; Arizona Alzheimer's Consortium.

Background: The distribution of the microscopic neuropathological lesions of neurodegenerative disorders have been extensively mapped within the brain but relatively little is known about their distribution in the peripheral nervous system. It has been conjectured that peripheral lesions might contribute to symptoms of autonomic nervous system dysfunction and that biopsy of peripheral sites might provide accurate and early diagnosis during life. The accuracy of the clinical diagnoses of PD and Alzheimer's disease (AD) have relatively high sensitivity but very low specificity, with an overall accuracy ranging between 65% and 75% at early-stage disease.

Methods: A sensitive immunohistochemical method for phosphorylated α -synuclein was used to stain sets of sections of spinal cord and body tissue from 41 different sites in the bodies of 92 subjects, including 23 normal elderly, 7 with incidental Lewy body disease (ILBD), 17 with PD, 9 with dementia with Lewy bodies (DLB), 19 with Alzheimer's disease with Lewy bodies (ADLB) and 17 with Alzheimer's disease with no Lewy bodies (ADNLB). The relative densities and frequencies of occurrence of phosphorylated α -synuclein histopathology (PASH) were tabulated and correlated with diagnostic category.

Results: The densities and frequencies of PASH were highest in the spinal cord, paraspinal sympathetic ganglia, vagus nerve, gastrointestinal tract and endocrine organs. The frequency of PASH within other organs and tissue types was much lower. Spinal cord and peripheral PASH was most common in subjects with PD and DLB, where it appears likely that it is universally widespread. Subjects with ILBD had lesser densities of PASH within all regions but had frequent involvement of the spinal cord and paraspinal sympathetic ganglia. Subjects with ADLB had infrequent involvement of the spinal cord and paraspinal sympathetic ganglia with rare involvement of end-organs. Within the gastrointestinal tract there was a rostrocaudal gradient of decreasing PASH frequency and density, with the lower esophagus and submandibular gland having the greatest involvement and the colon and rectum the lowest. Greater than 90% of subjects with PD or DLB were PASH-positive in the lower esophagus and submandibular gland.

Conclusions: These results provide a structural basis for autonomic dysfunction such as postural hypotension in subjects with Lewy body disorders and suggest that biopsy of the submandibular gland or esophagus would provide a diagnostic method for PD and DLB that would have high sensitivity and specificity.

RNA QUALITY AND GENE EXPRESSION IN HUMAN BRAIN TISSUE: EFFECTS OF POSTMORTEM INTERVAL AND FREEZE-THAW CYCLES. Birdsill AC, Walker DG, Lue LF, Beach TG, Sue LI, Beach TG. Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

Background: Banked human brain tissue is essential to the study of neurological disease but researchers using this resource must be aware of confounding effects related to pre-analytical factors including agonal physiological conditions, the duration of the postmortem interval (PMI) prior to tissue sampling and tissue storage conditions. Of all the molecular classes that might be analyzed, RNA has been considered to be one of the more volatile. There have been a number of published studies on the effect of PMI on overall RNA quality, generally assessed using measures of unbroken strand length, but the effects on mRNA or gene expression have not been examined in a comprehensive manner. Also, the effects of freeze-thaw cycles during storage have not been addressed adequately.

Methods: RNA was extracted from frozen cerebellar cortex samples from 79 human subjects with a variety of neuropathological diagnoses. The samples had been stored at -70 to -80 degrees C for between 1 and 16 years. Global RNA integrity measures including RIN and RNA concentration, determined using the Agilent 2100 Bioanalyzer. RNA from a subset of 39 cases, all with a diagnosis of Alzheimer's disease (AD), was subjected to a PCR-based gene expression array for 89 AD-genes (RT² ProfilerTM PCR Array: Human Alzheimer's Disease, SABiosciencesTM, Frederick, MD). The effects of freeze-thaw cycles were examined using 36 frozen cerebellar cortex samples from a single case with high RNA integrity. Samples were each subjected to 6 freeze-thaw cycles and global RNA integrity was assessed on a set of samples after each cycle.

Results: The PMI (range 1.5 to 45 hrs) correlated inversely with both RNA Integrity Number (RIN) ($r = -0.33$, $p < 0.002$) and RNA quantitative yield ($r = -0.25$, $p < 0.023$). Gene expression analysis showed a greater proportion of genes had decreased rather than increased expression with increasing PMI (65/89 vs 20/89; $p < 0.0001$). Of these, ADAM9, LPL, PRKCG, and SERPINA3 transcripts had significantly decreased expression with increasing PMI ($p < 0.01$). Successive freeze-thaw cycles had no significant effect on RIN but resulted in progressively decreased RNA quantitative yield ($r = .93$, $p < .008$). 80 genes had decreased expression with the number of cycles while only 5 had increased expression ($p < 0.0001$). Selective degradation of message for 21 genes occurred with successive freeze-thaw cycles, even after correction for total RNA concentration ($p < 0.01$).

Conclusions: Global RNA integrity declines progressively with increasing PMI and the apparent expression levels of individual genes tends to decline. Successive freeze-thaw cycles under these experimental conditions are associated with markedly decreased RNA yield and a generalized drop in apparent gene expression levels but do not affect RIN.

FREQUENCY OF ALZHEIMER'S DISEASE PATHOLOGY AT AUTOPSY IN PATIENTS WITH CLINICAL NORMAL PRESSURE HYDROCEPHALUS. Cabral D, Beach TG, Vedders L, Sue LI, Jacobson S, Myers K, Sabbagh MN. Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

Objectives: To determine the relative frequency of clinical normal pressure hydrocephalus (NPH) during life in cases with post-mortem dementia pathology and to ascertain the presence of Alzheimer's Disease (AD) neuropathology in NPH cases.

Background: Several studies have demonstrated the coexistence of AD in NPH based on cortical biopsies completed during shunt placement. The presence of AD pathology at autopsy in cases of clinical NPH has not been well studied.

Methods: We conducted a search of the Sun Health Research Institute Brain Donation Program database between 1/1/1997 and 4/1/09 to identify all cases with neuropathologic evidence of dementia as well as those cases of clinically diagnosed NPH. We reviewed the medical records and brain findings of each NPH case.

Results: Of the 761 cases autopsied over the study interval, 563 cases were found to have neuropathologically-defined dementia. AD was found exclusively in 313/563 (56%) cases with 94/563 cases having a secondary diagnosis of dementia. The remaining 156 cases had a sole neuropathologic cause with the following frequencies: 16/563 (2.7%) Vascular dementia; 8/563 (1.4%), Lewy Body Dementia; 3/563 (0.5%) Pick's Disease; and 70/563 (12%) Dementia NOS.

We identified 9/563 (1.6%) cases with a clinical diagnosis of NPH. Upon review of brain autopsy reports, 8/9 (89%) cases were found to have AD and 1/9 (11%) had progressive supranuclear palsy. Review of the medical records of the nine NPH cases revealed the following clinical comorbidities: 5/9 with AD; 1/9 with Parkinson's Disease (PD); 1/9 with Mild Cognitive Impairment (MCI); 1/9 with seizure disorder.

Conclusions: Post-mortem AD neuropathology was found commonly in patients diagnosed with clinical NPH during life. The findings support the theory of an AD-NPH syndrome.

THE ALZHEIMER'S QUESTIONNAIRE (AQ): A PILOT STUDY FOR A NEW INFORMANT-BASED DEMENTIA ASSESSMENT. Malek-Ahmadi M, Kataria R, Belden CM, Connor DJ, Pearson C, Jacobson S, Yaari R, Singh U, Sabbagh MN. Banner Sun Health Research Institute; Banner Alzheimer's Institute; Sierra Health; Arizona Alzheimer's Consortium.

Background: Making the clinical diagnosis of Alzheimer's disease (AD) in the primary care setting is difficult given that many physicians lack the resources necessary to effectively screen patients for cognitive problems. As a result, there is a need for a brief and accurate assessment of cognitive problems. The Alzheimer's Questionnaire (AQ) has been developed to meet this need by providing clinicians with a short and easily administered informant-based dementia assessment.

Methods: The AQ was administered to the informants of 99 individuals (41 AD, 38 MCI, 20 Normal Control [NC]) who were seen in 3 dementia clinics at their initial visit. NC individuals were recruited from a brain donation program in which the AQ was administered to their informant as part of their yearly assessment. Total score for the AQ (0-26) is based upon the sum of clinical symptom items in which the informant responds as being present. Clinical symptoms which are known to be highly predictive of the clinical AD diagnosis are given greater weight in the total AQ score. Between group analyses (NC vs MCI and MCI vs AD) were conducted on NC-MCI and MCI-AD pairs that were matched on age and education.

Results: The mean time of administration of the AQ was 2.6 ± 0.6 minutes. ANOVAs demonstrated statistically significant differences in AQ scores between cognitively normal individuals and MCI cases [$F = 65.40$, ($df = 1, 39$), $p < 0.0001$]. A similar result was found when MCI cases were compared against AD cases [$F = 32.32$, ($df = 1, 57$), $p < 0.0001$]. ROC curves for MCI cases versus NC individuals and MCI versus AD cases yielded AUC's of 0.98 (0.91, 1.00) and 0.85 (0.73, 0.93), respectively.

Conclusions: This pilot study indicates that the AQ is a sensitive measure for detecting cognitive impairment associated with Alzheimer's disease and is a short, easily administered tool. The AQ may be helpful to clinicians who must obtain an accurate, informant-based assessment of possible dementia in a short amount of time. This study also demonstrates the clinical validity of the AQ as it is able to accurately differentiate individuals along a continuum of cognitive impairment.

ECHOCARDIOGRAPHY VORTEX FORMATION TIME REVEALS CARDIAC DIASTOLIC TRANSMITRAL FLOW DYSFUNCTION IN ALZHEIMER'S DISEASE PATIENTS. Roher AE, Belohlavek M, Maarouf CL, Kokjohn TA, Garami Z, Bech TG, Sabbagh MN. Banner Sun Health Research Institute; Mayo Clinic Arizona; Midwestern University; Texas Medical Center; Arizona Alzheimer's Consortium.

Objective: There is considerable epidemiologic evidence that Alzheimer's disease is linked to cardiovascular risk factors and associated with an increased risk of symptomatic left ventricular dysfunction. Formation of a vortex alongside a diastolic jet signifies an efficient blood transport mechanism. Vortex formation time (VFT) is an index of optimal conditions for vortex formation. We hypothesized that Alzheimer's disease and its associated cardiovascular risk factors impair diastolic transmitral flow efficiency and, therefore, shift the VFT value out of its optimal range.

Methods: We recruited 45 patients in total, 22 patients (80.05 ± 6.73 years of age) with Alzheimer's disease diagnosed according to the American Psychiatric Association's criteria and 23 age-matched (76.48 ± 6.67 years of age, $P = 0.081$) individuals as a control group with cognitive function within normal limits. Echocardiography images were obtained using a Sonos 5500 ultrasound system with a 3.5 MHz transducer. Measurements included: peak transmitral flow velocities at mitral tip during early (E) and atrial (A) phases of left ventricular (LV) filling velocities, and calculation of E/A ratio; diastolic thickness of the interventricular septum (IVSd) and LV posterior wall (LVPWd); end-diastolic diameter of the LV (LVDd) and right ventricle (RVDd); left atrial diameter (LAd); LV end-diastolic volume (LVEDV) and end-systolic volume (ESV); LV stroke volume

Results: Of the 45 participants, there were 23 men (51%) and 22 women (49%). There were 15 men (68%), 7 women (32%) in the Alzheimer's disease group and 8 men (35%), 15 women (65%) in the control group. The mean values of mitral annular diameter when compared between the control and Alzheimer's disease groups were nearly identical, 2.75 ± 0.28 cm and 2.73 ± 0.40 cm, respectively ($P=0.725$). Time-velocity integral of the E-wave showed a trend towards a lower value in the Alzheimer's disease group (9.48 ± 2.74 cm) compared to the control group (10.91 ± 2.05 cm, $P=0.055$), whereas VFT was significantly lower in the Alzheimer's disease group as against the control group (3.33 ± 1.17 vs. 4.00 ± 0.85 , $P=0.018$).

Conclusions: Our study suggests that Alzheimer's disease patients have impaired transmitral flow efficiency of diastolic filling as measured by vortex formation time and compared to age-matched control subjects.

AMYLOID IMAGING WITH FLORBETAPIR F 18 (18F-AV-45) PET IN A SUBJECT WITH DOWN'S SYNDROME AND ALZHEIMER'S DISEASE AT THE END OF LIFE. Sabbagh MN, Jacobson SA, Sue LI, Cole L, Liebsack C, Charney AS, Beach TG. Banner Sun Health Research Institute; Arizona Alzheimer's Consortium.

Objective: To report the ability of florbetapir F 18 PET images to assess cortical β -amyloid deposition in a Down's syndrome (DS) subject with Alzheimer's disease (AD) proximate to death.

Background: Molecular imaging of amyloid deposition *in vivo* has the potential to improve clinical diagnostic accuracy. Florbetapir is under development as a candidate amyloid PET biomarker with adequate performance characteristics to correlate PET images with histopathological findings at autopsy. Since DS patients develop AD, amyloid imaging could be used to detect AD pathology in DS subjects.

Design/Methods: A 55 year old subject with DS presented 5 years prior to death with progressive cognitive decline. Given the low baseline function, the decline was documented from family members by progressive loss of IADLs and ADLs. Eventually, the subject was non-testable, and the last MMSE was recorded as 0. The DS subject was enrolled in the florbetapir histopathology study. The subject received a 10 minute PET image after iv injection of 10 mCi (370 MBq) of florbetapir. Each image was rated visually using a semi-qualitative scale (0 – 4) for overall ligand retention in cortical gray matter. Independently a semi-automated algorithm calculated standard uptake values (SUV) in pre-defined anatomically relevant cortical regions, relative to cerebellar gray matter (SUV_r). The subject expired 14 days after imaging. The brain was collected at autopsy for neuropathological analysis. Neuropathologic studies will be performed without knowledge of the clinical and PET data.

Results: The interval from imaging to death was 14 days. Visual ratings of the intensity of florbetapir signal across the 6 PET scans ranged from 0 (no amyloid) to 4 (maximal amyloid). There was moderate uptake of florbetapir in the frontal cortex, mild uptake occipital and white matter and minimal uptake in the temporal cortices but no significant uptake in the parietal cortices by visual inspection. The co-registered CT revealed underlying atrophy and ex vacuo changes to the ventricles. Autopsy results and correlation to imaging findings will be presented.

Conclusions/Relevance: This is the first report of florbetapir imaging in a DS subject with AD. Since the images were gathered proximate to death, there is an opportunity to correlate imaging findings with pathological features at autopsy. Molecular imaging with florbetapir could provide important information about brain β -amyloid deposition in cortical gray matter in advanced dementia but the pattern may be different in DS/AD compared to idiopathic AD.

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CEREBROVASCULAR RISK FACTORS INFLUENCE AGE-RELATED MEMORY DECLINE. Caselli RJ, Dueck AC, Locke DEC, Sabbagh MN, Ahern GL, Rapcsak SZ, Baxter LC, Yaari R, Woodruff BK, Hoffman-Snyder C, Findley S, Reiman EM. Mayo Clinic Arizona; Banner Sun Health Research Institute; University of Arizona; Barrow Neurological Institute; Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.

Objective: To explore the possible influence of cerebrovascular (CV) risk factors on age related memory decline.

Background: APOE e4 is a major risk factor for Alzheimer's disease. Even in the absence of symptomatic impairment, memory declines in e4 carriers on the Auditory Verbal Memory Test (AVLT) Long Term Memory score prior to age 60 years (Caselli et al, 2009). CV disease also can lead to cognitive decline, so we explored whether CV risk factors in the absence of symptomatic CV disease might further influence age-related memory decline.

Methods: Participants were cognitively normal, age 21-97 years, recruited through local ads, grouped by APOE e4 genotype, and received the AVLT (as part of a larger neuropsychological battery) every 1-2 years. Hypertension (HTN), diabetes mellitus (DM), hypercholesterolemia (CHOL), and prior cigarette use (CIG) were treated as dichotomized variables. We estimated the longitudinal effect of age using statistical models that simultaneously modeled the cross sectional and longitudinal effects of age on AVLT-LTM by APOE e4 carrier status, each CV risk factor, and the interaction between the two. The same approach was also used for any combination of CV risk factors (CV-all) and for obesity (OB). Those who developed MCI, dementia, or stroke during followup were excluded.

Results: 313 APOE e4 carriers and 494 noncarriers did not differ by age (mean 60 +/- 13 years), education (mean 15.4 +/- 2.6 years), or gender (69% women). DM ($p=.003$), CIG ($p=0.01$), and OB ($p=.03$) were less prevalent in e4 carriers. In quadratic models only APOE e4 carrier status showed a main effect with age-related LTM decline. In linear models, significant interactions with APOE and age were found for CHOL ($p=.05$), CIG ($p=.007$), DM ($p=.07$), CV-all ($p=.04$), and OB ($p=.03$).

Conclusions: CV risk factors in general, as well as OB may further influence age-related memory decline in APOE e4 carriers.

ANXIETY IS ASSOCIATED WITH MILD COGNITIVE IMPAIRMENT: A POPULATION-BASED STUDY. Geda YE, Obermeier A, Roberts RO, Knopman DS, Pankratz VS, Boeve BF, Petersen RC. Mayo Clinic Rochester; Paracelsus Medical School, Salzburg, Austria; Arizona Alzheimer's Consortium.

Background: Little is known about the prevalence of anxiety in mild cognitive impairment (MCI). Therefore, we investigated the association of anxiety with MCI in a population-based setting.

Methods: We conducted a case-control study derived from the population-based Mayo Clinic Study of Aging in Olmsted County, Minnesota. A random sample of 1,962 elderly participants aged 70-90 years (n = 1,635 cognitively normal persons and n = 327 subjects with MCI) constituted the sample for this study. We measured the prevalence of anxiety using the Beck Anxiety Inventory (BAI) and used a cut-off score of >9. A score of 0-21 indicates low anxiety; a score of 22-35 indicates moderate anxiety; a score of 36-63 indicates a high level of anxiety. We then compared the prevalence of anxiety in subjects with MCI to the prevalence in cognitively normal persons. Multivariable logistic regression analyses were conducted to compute odds ratios (OR) and 95% confidence intervals (CI).

Results: Among 1,635 cognitively normal individuals, the median age was 79.6 years (range, 70.5 - 91.1 years); 827 (50.6%) of them were women. The BAI score was >9 in 115 individuals (7.0%). Among the 327 subjects with MCI, the median age was 82.7 (range, 70.9 - 91.8 years); 135 (41.3%) of them were women. The BAI score was >9 in 41 individuals (12.5%). After adjusting for age (continuous), sex, education (continuous in years), and Charlson Index (continuous), anxiety was significantly more prevalent in MCI than among cognitively normal persons (OR [95% CI] = 1.69 [1.14, 2.51]; p = 0.008).

Conclusions: In a population-based setting, the prevalence of anxiety is significantly higher in MCI than in cognitively normal persons. However, our study did not address the causal direction of this association.

GREY MATTER VOLUME REDUCTIONS IN HEALTHY APOE-e4 CARRIERS: COMPARISON OF DARTEL AND STANDARD SPM NORMALIZATION METHODS.

Stonnington CM, Chen K, Lee W, Alexander GE, Reiman EM. Mayo Clinic Arizona; Banner Alzheimer's Institute; Banner Good Samaritan Medical Center; University of Arizona; Arizona Alzheimer's Consortium.

Background: There are conflicting reports of MRI findings in presymptomatic individuals with 0, 1 or 2 copies of apolipoprotein E (APOE) e4 alleles. DARTEL is a recently introduced integrated non-linear warping and brain tissue segmentation technique that improves the sensitivity and specificity in detecting disease related subtle difference which might be undetectable using standard SPM normalization and voxel based morphometry (VBM).

Methods: Subjects were 31 e4 homozygotes (HM), 42 e4 heterozygotes (HT), and 75 e4 noncarriers (NC) with baseline MRIs, assessed on 2 different scanners, matched for age (mean 57 years), sex and education (mean 15.7 years), and enrolled in the APOE longitudinal cohort study (R01MH57899-01). After segmentation and normalization with both DARTEL and standard SPM5 VBM, smoothed, modulated GM images were analyzed with SPM general linear model (GLM) to compare APOE groups in a factorial design, modeling for the two scanners, with $p < .001$ uncorrected threshold. We then again used SPM GLM to compare the interaction between detected group differences and the standard VBM and DARTEL procedures.

Results: With DARTEL, regional GM volume reductions at the right and left parahippocampal, left parietal, and left midtemporal regions were found for HM compared to NC; and at the left parahippocampal region for HT compared to NC. There were significantly greater detected GM reductions in the parietal ($T = 3.49$, $p < .001$, at x, y, z -34, -54, 44), temporal ($T = 3.25$, $p < .001$, at x, y, z -60, -38, 24), and middle cingulate ($T = 3.50$, $p < .001$, at x, y, z 2, 30, 36) regions for HM compared to NC using DARTEL than with standard VBM. For HT compared to NC, several regions (precuneus, parietal, cingulate, insula, parahippocampal, temporal, and cerebellar) showed significantly greater GM reductions detected by DARTEL than by standard VBM. Conversely, there were no regions in which standard VBM showed greater GM volume reductions than DARTEL.

Conclusions: These findings suggest that DARTEL procedure is more sensitive than standard VBM to discern presymptomatic imaging changes.

A SURVEY OF THE ALZGENE DATABASE FOR GENETIC RISK FACTORS IN ALZHEIMER'S DISEASE. Corneveaux JJ, Allen AN, Pruzin JJ, Chewning K, Villa SE, Meechoovet B, Gerber JD, Frost D, Benson HL, Heward CB, Hardy J, Myers AJ, Craig DW, Van Keuren-Jensen KR, Dunckley T, Reiman EM, Huentelman, MJ. Translational Genomics Research Institute; Kronos Life Sciences; University College of London; University of Miami; University of Arizona; Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.

Background: To date, the apolipoprotein (*APOE*) epsilon 4 variant is the only major known genetic risk factor for late onset Alzheimer's disease (LOAD); however, *APOE* ϵ 4 is not the only genetic risk factor. Numerous genome wide association studies (GWAS) have been undertaken to examine and uncover additional genetic loci, and the AlzGene database has been developed to summarize the most replicated findings. Despite the utility of the AlzGene database, many of the studies within draw from clinically diagnosed samples rather than samples whose brains were pathologically verified. We undertook a large GWAS utilizing strict neuropathological conditions in order to better understand the genetics of LOAD.

Methods: We conducted a GWAS utilizing 1,610 clinically and neuropathologically characterized expired brain donors using the Affymetrix SNP 6.0 arrays. Study participants were self-defined ethnicity of European, neuropathologically confirmed AD or no neuropathology present, and age of death greater than 65. We carried out logistic regression using PLINK controlling for gender and population structure.

Results: We find a markedly higher odds ratio than reported in the AlzGene metaanalysis of 5.5 for *APOE* ϵ 4 heterozygotes and 20.6 for *APOE* ϵ 4 homozygotes. We observe two additional highly significant loci at *TOMM40* ($p=9.805 \times 10^{-20}$) and *APOC1* ($p=2.049 \times 10^{-45}$) that flank *APOE* and in past literature have been attributed to linkage disequilibrium (LD) with the ϵ 4 variant. We examined 34 of the top most replicated genetic markers for AD from the AlzGene database and find significant results for *CRI* (rs6656401; $p=0.008$; OR=1.28), *PICALM* (rs541458; $p=0.010$; OR=0.81), *LOC651924* (rs6907175; $p=0.027$; OR=1.18), *ACE* (rs1800764; $p=0.030$; OR=0.85), *CST3* (rs1064039; $p=0.033$; OR 0.83) and *CLU* (rs11136000; $p=0.040$; OR=0.86).

Conclusions: We have leveraged neuropathological phenotyping and strict sample quality control, which we argue provides additional power to detect subtle associations due to improved classification of AD cases and controls. We observe odds ratios in the AlzGene loci, in all cases, equal to or marginally greater than the odds ratios observed in the original studies, illustrating the utility of pathological sample collections for AD.

ASSOCIATION BETWEEN A POSSIBLY PROTECTIVE GAB2 HAPLOTYPE AND HIGHER GLUCOSE METABOLISM IN ALZHEIMER'S DISEASE-AFFECTED BRAIN REGIONS IN COGNITIVELY NORMAL APOE ϵ 4 CARRIERS. Liang WS, Chen K, Lee W, Sidhar K, Corneveaux JJ, Allen A, Villa S, Meechoveet B, Pruzin J, Bandy D, Reeder SA, Venditti JM, Fleisher AS, Langbaum JBS, Huentelman MJ, Jensen K, Caselli RJ, Reiman EM. Translational Genomics Research Institute; Banner Alzheimer's Institute; Banner Good Samaritan Medical Center; Arizona Alzheimer's Consortium.

Objective: In a genome-wide association study (GWAS) of late-onset Alzheimer's disease (AD), we found an association between common haplotypes of the GAB2 gene and AD risk in carriers of the apolipoprotein E (APOE) ϵ 4 allele, the major late-onset AD susceptibility factor. This finding has been confirmed in some studies but not in others. We previously proposed the use of fluorodeoxyglucose positron emission tomography (FDG-PET) measurements as a quantitative pre-symptomatic endophenotype, more closely related to disease risk than the clinical syndrome itself, to help evaluate putative genetic and non-genetic modifiers of AD risk.

Methods: In this study, we examined the relationship between the presence or absence of the relatively protective GAB2 haplotype and FDG-PET measurements of the cerebral metabolic rate for glucose (CMRgl) in several AD-affected brain regions in 158 cognitively normal late-middle-aged APOE ϵ 4 homozygotes, heterozygotes, and non-carriers. GAB2 haplotypes were characterized using Affymetrix Genome-Wide Human SNP 6.0 Array data from each of these subjects.

Results: As predicted, the possibly protective GAB2 haplotype was associated with higher CMRgl in AD-affected brain regions in APOE ϵ 4 carriers.

Conclusions: While additional studies are needed, this study supports the association between the possibly protective GAB2 haplotype and the risk of late-onset AD in APOE ϵ 4 carriers. It also supports the use of brain-imaging endophenotypes to help assess possible modifiers of AD risk.

ASSOCIATION OF *TOMM40* AND *APOC1* WITH ALTERED ALZHEIMER'S DISEASE RISK IN APOE ε3 HOMOZYGOTES. Pruzin JJ, Corneveaux JJ, Allen AN, Chewning K, Villa SE, Meechoovet B, Gerber JD, Frost D, Benson HL, Heward CB, Hardy J, Myers AJ, Craig DW, Van Keuren-Jensen KR, Dunckley T, Reiman EM, Huentelman, MJ. Translational Genomics Research Institute; Kronos Life Sciences; University College of London; University of Miami; University of Arizona; Banner Alzheimer's Institute; Arizona Alzheimer's Consortium.

Background: The apolipoprotein (*APOE*) epsilon 4 genotype is one of the most replicated and significant genetic risk factors found in common complex human disease, yielding a very significant ($p=1.8 \times 10^{-157}$) association to Alzheimer's disease (AD) in a large Genome Wide Association Study (GWAS) (Harold et al., 2009). While it is clear that the polymorphism contributes a high degree of risk for developing AD it is also known that the epsilon 4 genotype is neither necessary or sufficient to develop AD. The search for other genetic risk factors has produced a handful of candidates, some of which rest in close proximity to the *APOE* genetic locus. Signals from regions near *APOE* are often dismissed due to their putative linkage disequilibrium (LD) with the known risk factor, assumed to be driving the association. One such association proximal to *APOE*, previously ignored but recently suggested to be an important risk factor, is a variable length poly T repeat in the *TOMM40* gene (Roses et al., 2009). Another associated gene previously attributed to proximity to *APOE* is *APOC1*. To help determine if association signals near *TOMM40* and *APOC1* are indicative of independent risk factors for AD, or if LD with *APOE* is driving the association, we utilized data from our recent GWAS performed on post-mortem pathologically verified individuals and then stratified groups by APOE status to analyze the contribution of risk by *TOMM40* and *APOC1*.

Methods: GWAS data was derived from 1,610 clinically and neuropathologically characterized expired brain donors using the Affymetrix SNP 6.0 arrays. Study participants were self-defined ethnicity of European, neuropathologically confirmed AD or no neuropathology present, and age of death greater than 65. We carried out logistic regression using PLINK controlling for gender and population structure. We then stratified the cohort by APOE4 status to specifically look at signals coming from *APOC1* and *TOMM40* and analyze their effects independent or in conjunction with APOE.

Results: When examined independently, we find a significant association with both rs1160985 ($p=9.805 \times 10^{-20}$) a SNP within *TOMM40*, and rs4420638 ($p=2.049 \times 10^{-45}$) a SNP just upstream of *APOC1*. When these SNPs are analyzed after stratifying cases and controls by APOE status we find significant associations with both rs1160985 ($p=0.0022$) and rs4420638 ($p=0.00025$) in people who are homozygous for the risk neutral APOE3 allele. In relation to rs4420638, there is a less, but still significant association ($p=0.029$) in people with one APOE4 allele and one APOE3 allele. There are no significant associations with either SNP in people homozygous for the APOE4 allele or those with one APOE3 allele and one APOE2 allele.

Conclusions: Our study suggests *APOC1* and *TOMM40* are significantly associated with LOAD independent of APOE4. This is demonstrated by the significant effects of the SNPs within the two genes when analyzed in risk neutral APOE3 homozygotes. These SNPs have a much greater affect in the absence of the proven risk factor. The disputed LD structure of the nearby genes coupled with the fact that all three genes have differing degrees of protective and risk-conferring alleles, warrant further investigation by targeted sequencing. Deep sequencing of a large sample size will clearly delineate the LD of genes in the region providing a valuable tool for researchers studying the region as the prominent AD risk locus. Furthermore, sequencing individuals with different combinations of the AD associated genes *TOMM40*, *APOE*, and *APOC1* will help parse which genes confer what degree of risk as well as provide clues on how the three genes may interact to determine an individual's overall risk for developing LOAD.

IDENTIFICATION OF APOE GENOTYPES USING INDEXED NEXT GENERATION SEQUENCING. Reiman R, Pruzin JJ, Corneveaux JJ, Huentelman MJ. Translational Genomics Research Institute; Arizona Alzheimer's Consortium.

Background: Apolipoprotein E (APOE) is the most common genetic association with Late Onset Alzheimer's Disease (AD), with a specific degree of relative risk and of disease-onset associated with each of three alleles (APOE ϵ 2, APOE ϵ 3, APOE ϵ 4). Assessing and controlling for APOE status during the genetic study of AD is essential. The current approaches utilized to assess APOE status incorporate the use of genotyping of the two functional polymorphisms. Interestingly some approaches are known to be susceptible to errors induced by neighboring polymorphisms. One such example is the presence of a low frequency SNP that alters a RFLP site within APOE (Rihn *et al.* 2009). Our aim during this study was to develop a high throughput, high accuracy, and low cost approach for genotyping APOE through the use of indexed next generation sequencing.

Methods: Using DNA from twelve individuals whose APOE genotypes were known through previous Sanger-based sequencing, we amplified the APOE region (1kb) using PCR, indexed each sample's amplicons with one of twelve unique Illumina bar-codes, pooled all twelve samples together in one lane of an 8-lane flow cell and sequenced them on an Illumina Genome Analyzer II instrument. Blinded from the established genotypes, we sorted the data by each unique oligonucleotide bar-code and assessed each individual's APOE genotype based on variants at SNPs rs429358 and rs7412.

Results: In samples with high sequencing coverage we determined APOE genotype accurately based on SNPs rs429358 and rs7412. One sample did not have sufficient coverage to make a determination due to poor PCR yield of the targeted region in sample preparation.

Conclusions: The data suggests that with sufficient coverage we are able to multiplex the sequencing of at least 12 individuals and achieve accurate APOE genotyping. We believe this approach can be expanded upon to yield an ability to sequence 96 individuals per sequencer lane thereby allowing us to reach our goals of high accuracy and low cost APOE genotyping.

MULTIVARIATE REGIONAL NETWORK PATTERN OF MRI GRAY MATTER PRECEDING CONVERSION TO DEMENTIA IN AMNESTIC MILD COGNITIVE IMPAIRMENT. Bergfield KL, Hanson KD, Chen K, Reiman EM, Bernstein MA, Kormak J, Harvey D, Schuff NW, Thompson PM, Weiner MW, Jack Jr. CR, Moeller Jr, Alexander GE. University of Arizona; Banner Alzheimer's Institute; Banner Good Samaritan Medical Center; Mayo Clinic, Rochester; University of California San Francisco; University of California Davis; Veterans Affairs Medical Center, San Francisco; University of California Los Angeles; Columbia University; Arizona Alzheimer's Consortium.

Background: Previous studies in Alzheimer's disease (AD) patients have demonstrated brain volume reductions on magnetic resonance imaging (MRI), with temporal lobe structures preferentially affected compared to healthy aging. Amnesic mild cognitive impairment (aMCI) is viewed as a transitional stage between healthy cognitive aging and AD, where individuals with aMCI develop dementia at a higher rate than the general elderly population. We sought to identify the characteristic regional pattern of gray matter atrophy associated with aMCI in those individuals known to subsequently convert to dementia.

Methods: We used voxel-based morphometry (VBM) with multivariate network analysis to identify the regional pattern of gray matter associated with aMCI in individuals who converted to dementia in the 3 years after their baseline assessment compared to healthy controls. Analyses included 80 aMCI converters (mean age=75.6±7.5; M/F=48/32, mean years to conversion=1.41±0.61, range=0.4-3.1 years) selected from a cohort of 375 participants with aMCI with follow up ranging from 6-months up to 3-years as part of the Alzheimer's Disease Neuroimaging Initiative (www.loni.ucla.edu/ADNI). A group of 159 healthy controls (mean age=75.2±4.9; M/F=96/63) were matched to the aMCI converters in age, gender, and years of education. Using volumetric T1 MPRAGE MRIs obtained at baseline, VBM processing was performed with statistical parametric mapping (SPM5) to produce smoothed gray matter volume maps. Multivariate Scaled Subprofile Model (SSM; Moeller et al., 1987; Alexander and Moeller, 1994) analysis was performed to identify a regional pattern of gray matter reductions that distinguished the aMCI converters from healthy controls.

Results: SSM analysis of the aMCI and control groups combined identified a linear combination of four component patterns that best distinguished the aMCI converters from healthy controls ($R^2=0.37$, $p<0.000001$) with each significantly contributing to the model. This combined pattern was characterized mainly by bilateral reductions in the medial and lateral temporal lobes including in the hippocampus, with small areas of relative preservation in bilateral mid and anterior cingulate and in the vicinity of the basal ganglia.

Conclusions: The results indicate a regionally distributed pattern of MRI gray matter atrophy that precedes the conversion to dementia in individuals with aMCI and includes reductions in brain regions that are known to be affected early in AD. Investigating network patterns of MRI brain atrophy in those destined to develop dementia may aid efforts toward identifying individuals with aMCI at greatest risk for conversion to AD within the first few years of follow up.

SLEEP CHARACTERISTICS IN OLDER CHILDREN WITH DOWN SYNDROME Breslin JH, Mason GM, Edgin JO, Bootzin RR, Goodwin JL, Nadel L. University of Arizona; Arizona Alzheimer's Consortium.

Background: Children with Down syndrome (DS) are susceptible to the development of obstructive sleep apnea (OSA) due to midfacial and mandibular hypoplasia, glossoptosis, and adenoidal and tonsillar hypertrophy. Other predisposing factors to OSA in DS include obesity, hypothyroidism, and generalized hypotonia. Laboratory polysomnographic (PSG) studies have reported the presence of OSA in younger children with DS, estimated to be somewhere between 30-79% (de Miguel-Díez et al., 2003; Dyken et al., 2003; Fitzgerald et al., 2007; Schott et al., 2006). Problems with bedtime settling, sleep onset, sleep maintenance, and early morning waking have also been reported in children with DS (Stores et al., 1998; Cotton & Richdale, 2006; Levanon et al., 1999).

Methods: We performed in-home ambulatory overnight polysomnography in 17 older children with DS (age M = 12.73; 7 girls).

Results: Although nearly all of the children had an adenotonsillectomy prior to the study, we found that 15 of the 17 children (88%) met criteria for pediatric OSA (AHI \geq 1.5). Six of these were classified as mild (AHI > 1.5), three as moderate (AHI > 5), and six were severe (AHI > 10). The mean arousal index was 4.38, and the mean arterial oxygen saturation low point was 85%. Our sample did not appear to have difficulties falling asleep (SOL M = 17.44), but did have some difficulty maintaining asleep (WASO M = 48.15).

Conclusions: We found a high rate of OSA in an older sample of children with DS, nearly all of whom had had an adenotonsillectomy. This finding suggests that surgery does not completely eliminate OSA in this population. We also found some evidence of sleep maintenance problems.

ANALYSIS OF THE MONTREAL COGNITIVE ASSESSMENT (MOCA) AND ITS INDIVIDUAL DOMAINS VERSUS THE MINI MENTAL STATE EXAMINATION IN COGNITIVELY IMPAIRED VERSUS COGNITIVELY NORMAL SUBJECTS AS ASSESSED BY NEUROPSYCHOLOGICAL TESTING. Damian AM, Jacobson SA, Belden C, Shill H, Sabbagh MN, Vedders L, Hentz JG, Caviness J and Adler CH. University of Arizona in Partnership with Arizona State University; Banner Sun Health Research Institute; Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

Background: Several studies have shown that the MoCA is superior to the MMSE in the detection of mild cognitive impairment and non-cortical dementias such as PDD. Our experience suggests that the individual items on the MoCA contribute differently to its sensitivity.

Methods: 135 consecutive Brain Bank subjects were administered the MoCA by a single evaluator (SJ) and the MMSE by a project nurse. Subjects were classified as cognitively impaired on the basis of neuropsychological testing, and specific diagnoses were made based on consensus conference diagnosis following neurological exam, movement exam, and neuropsychological exam.

Results: 89 subjects were cognitively normal (mean age= 77.7), 46 cognitively impaired (20 dementia, 26 MCI) (mean age= 79.4). Age range 46-100. ROC analysis showed that the area under the curve of the MMSE was completely contained within that of the MoCA. MoCA (cutoff score=26) had a sensitivity of 98% and a specificity of 52% for cognitive impairment. The MMSE, (cutoff score=28 to maximize Youden Index), had a sensitivity 76% and a specificity of 75%). Recall had the best performance among the individual items on the MMSE, and Orientation had the best performance among the individual items on the MoCA. The best performance was obtained by using a weighted combination of four items (2*Orientation + Recall + Language + 0.5*Visuospatial, AUC 0.94). Including additional items did not substantially improve the four-item model

Conclusions: Findings were in agreement with earlier studies showing better sensitivity of the MoCA in detecting cognitive impairment. Our ROC analysis suggested that the MoCA made significant improvements in specificity as well. Individual domains on the MoCA and MMSE made substantially different contributions to the instrument's sensitivity, suggesting the possibility of an abbreviated screening tool.

DISTINGUISHING THE ROLES OF PARAHIPPOCAMPAL CORTEX AND HIPPOCAMPUS DURING OBJECT-SCENE RECOGNITION. Duke D, Lin C-Y, Kawa K, Nadel L, Ryan L. University of Western Ontario, Canada; National Cheng Kung University, Taiwan, Republic of China; University of Arizona; Arizona Alzheimer's Consortium.

Background: Hayes et al. (2007) demonstrated that object recognition decreases when objects are studied in a semantically-related scene and then tested on a white background, compared to objects tested in the same context. During study, parahippocampal cortex (PHC) activated during object-scene presentation and predicted subsequent object recognition. PHC also re-activated during recognition testing, even when objects were tested on a white background. These results suggested that PHC contributes to object-scene binding and acts to reinstate that scene context during subsequent retrieval, even when the context is no longer present. Left unanswered by this study is whether PHC binds the specific object-scene pairs, or whether PHC activates when an object is presented in any semantically-related scene, regardless of the specific visual details of that scene (suggested by Bar & Aminoff, 2003).

Methods: The present fMRI study involved young adults making old/new recognition judgments for objects studied in semantically-related scenes and then tested in four context conditions: i) the identical scene, (ii) a novel but equally related scene, (iii) a familiar (old) but recombined scene, or iv) a white background.

Results: During recognition, PHC activity was equivalent for all three object-scene test conditions, regardless of whether the original object-scene pair was presented. In contrast, bilateral hippocampus activated optimally when the object was presented once again in the identical scene, compared to a familiar but recombined scene.

Conclusions: These findings suggest that PHC may respond to objects presented in any semantically-related scene, while hippocampus codes for visually-specific object-scene pairs.

FACE MEMORY LOSS AND FACE MEMORY DISTORTION IN FRONTOTEMPORAL DEMENTIA. Edmonds EC, Rapcsak SZ, Bartlett JC, Glisky EL. University of Arizona; Veterans Administration Medical Center; University of Texas; Arizona Alzheimer's Consortium.

Background: Previous studies of patients with focal brain lesions have demonstrated that accurate face recognition involves an interaction between memory and executive control systems. This study examined the behavioral and neural correlates of face recognition impairment in patients with frontotemporal dementia (FTD). We hypothesized that executive dysfunction would result in memory distortions beyond what could be explained by face memory loss alone.

Methods: Participants included two patients with FTD. Voxel-based morphometry revealed temporal lobe atrophy in Patient 1 and both temporal and frontal lobe atrophy in Patient 2. Participants completed a battery of anterograde face memory tests (two-alternative forced-choice and yes/no tests using a variety of lures), and a retrograde fame judgment test using both famous and unfamiliar faces.

Results: Participants demonstrated comparable face memory impairment on the forced-choice test and equally poor memory discrimination on anterograde yes/no tests. Patient 1 showed a pattern of responses consistent with a guessing strategy, while Patient 2 demonstrated a liberal response bias resulting in profound false recognition for category-consistent lures. Patient 2 also demonstrated high false alarm rates on the retrograde memory test, identifying unfamiliar faces as “famous.”

Conclusions: The presence or absence of frontal dysfunction profoundly alters the clinical manifestations of the face memory deficit in FTD, as it is associated with increased memory distortions and an overreliance on general or categorical information when making recognition decisions in both the anterograde and retrograde domains. These findings are consistent with the differential impact of frontal versus temporal lobe damage on face memory documented in patients with focal lesions.

NETWORK ANALYSIS OF MRI GRAY MATTER IN AMNESTIC MILD COGNITIVE IMPAIRMENT: RELATION TO RATES OF COGNITIVE DECLINE AND CONVERSION TO DEMENTIA. Hanson KD, Chen K, Ryan L, Glisky EL, Reiman EM, Bernstein MA, Kornak J, Harvey DJ, Schuff NW, Jack Jr. CR, Thompson PM, Weiner MW, Alexander GE. University of Arizona; Banner Alzheimer's Institute, Banner Good Samaritan Medical Center; Mayo Clinic Rochester; University of California San Francisco; University of California Davis; Veterans Affairs Medical Center, San Francisco; University of California Los Angeles; Arizona Alzheimer's Consortium.

Background: Amnesic mild cognitive impairment (aMCI) is thought to be a transitional stage between normal aging and the dementia of Alzheimer's disease (AD). We used voxel-based morphometry (VBM) with multivariate network analysis to determine if regional patterns of gray matter from magnetic resonance images (MRI) could predict subsequent declines in cognitive performance and conversion to AD in individuals with aMCI.

Methods: Analyses included 100 AD patients (mean age=75.7±7.2; M/F=50/50), 100 individuals with aMCI (mean age=74.9±7.1; M/F=50/50) and 100 healthy controls (HC; mean age=75.5±4.9; M/F=50/50) from the Alzheimer's Disease Neuroimaging Initiative (www.loni.ucla.edu/ADNI). The groups did not differ in age, years of education, or gender and the aMCI group included participants who did not convert to dementia during the first 12 months of follow up. Baseline volumetric T1 MPRAGE MRIs were processed using VBM with statistical parametric mapping (SPM5). Neuropsychological performance was assessed at baseline and after a 12-month follow-up and 85 participants in the aMCI group were followed additionally over an average of 21.8±2.9 months post-baseline.

Results: Using multivariate network analysis with the scaled subprofile model (SSM; Moeller et al., 1987; Alexander and Moeller, 1994) for all 300 participants combined produced a regional pattern of gray matter reductions associated with group membership ($R^2=0.34$, $p \leq 0.000001$), reflecting the continuum of clinical severity from HC to aMCI to AD. This pattern showed gray matter reductions in bilateral mid and inferior temporal cortices, including in hippocampal and parahippocampal regions, with areas of relative preservation in the anterior and mid cingulate and bilateral superior, mid, and inferior frontal cortices. After we controlled for baseline levels of cognitive performance, greater group-related pattern expression was associated with greater 12-month declines in attention ($p \leq 0.00002$) and language ($p \leq 0.025$) functions, but not in memory ($p=ns$) in the aMCI group. The association with declines in language was reduced to non-significance after controlling for attentional decline ($p=ns$). Further in the aMCI participants with extended follow up, higher network pattern scores were associated with conversion to dementia ($p \leq 0.009$).

Conclusions: The findings suggest that individual differences in network patterns of gray matter atrophy may assist in predicting subsequent cognitive decline in aMCI, where attentional decline may precede conversion to dementia. MRI with voxel-based network analyses may aid efforts toward identifying those individuals who progress to dementia and may benefit from early treatment.

THE EFFECTS OF SEMANTIC RELATEDNESS ON CONTEXT-SPECIFIC OBJECT RECOGNITION. Kawa K, Duke D, Parch J, Cardoza J, Nadel L, Ryan L. University of Arizona; University of Western Ontario, Canada; Arizona Alzheimer's Consortium.

Background: Hayes, Nadel, and Ryan (2007) demonstrated that object recognition performance decreased by approximately 15% following a change in context from study to test, specifically, when objects studied in a complex scene were then tested on a white background. The decrement was observed regardless of whether encoding was intentional or incidental, suggesting automatic binding between the object and the scene. This automatic binding may have occurred because the objects were presented in scenes that were strongly semantically related to the object – a vase on a coffee table, a lamp on an office desk, etc.

Methods: To investigate the influence of semantic relatedness on context-specific object recognition, the present study varied the specific context from study to test while maintaining semantic relatedness between the object and the context. Household objects (e.g., teapot) were presented in a strongly semantically related scene (e.g., a kitchen). The objects were then tested either in the identical context (the same kitchen), a semantically similar context (another kitchen), a different but equally semantically related context (a dining room), or on a white background.

Results: Results showed a stepwise decrease in recognition performance – the same kitchen > another kitchen > a dining room > a white background. Thus, recognition was supported by both the semantic similarity of the context from study to test, as well as the specific visual details of the scene.

Conclusions: While optimal recognition occurs when the exact same context is presented, other semantically appropriate contexts may still be used to aid in retrieval of episodic information.

REGIONAL REDUCTION OF CORTICAL THICKNESS IN COGNITIVELY NORMAL LATE MIDDLE AGED ADULTS WITH APOE E4. Lin K, Ashish D, chen K, Bergfield KL, Caselli RJ, Reiman EM, Alexander GE. University of Arizona; Banner Alzheimer's Institute; Mayo Clinic Arizona; Arizona Alzheimer's Consortium.

Background: In previous studies, we have demonstrated reductions in cerebral metabolism in cognitively normal late middle-aged adults with the apolipoprotein E (APOE) ϵ 4 allele compared to ϵ 4 non-carriers, involving brain regions typically associated with the effects of Alzheimer's disease (AD) as well as healthy aging (Reiman et al., 1996, 2004, 2005). We now investigate differences between APOE ϵ 4 carriers and non-carriers in regional measures of cortical thickness assessed with magnetic resonance imaging (MRI) in a group of cognitively normal late-middle aged adults.

Methods: All participants had a reported family history of dementia, had no cognitive difficulties or complaints, and included 19 individuals with two copies (mean age=57.0 \pm 4.9; M/F=6/13), 26 with one copy (mean age=57.9 \pm 4.1; M/F=8/18), and 35 with no copies [non-carriers (NC)]; mean age=57.3 \pm 5.3; M/F=10/25] of the ϵ 4 allele. The groups did not differ in age, gender, or years of education. Volumetric T1 MRI scans were processed using Freesurfer software (Fischl et al., 1999; Dale et al., 1999) to measure cortical thickness in 35 regions of interest (ROI) from each hemisphere.

Results: Repeated-measures analyses with group as the between-subject and hemisphere as a repeated-measures factor indicated bilateral main effects for group ($p < 0.05$, uncorrected for multiple omnibus tests) with less cortical thickness in the APOE ϵ 4 carriers combined ($n=45$) compared to non-carriers ($n=35$) in caudal and rostral anterior cingulate, fusiform, medial orbitofrontal, inferior and superior temporal, inferior parietal, and lateral occipital regions ($0.007 < p < 0.05$). There were no significant group by hemisphere interactions. APOE ϵ 4 gene dose (the number of ϵ 4 alleles in a person's APOE genotype) was associated with corresponding reductions in cortical thickness in inferior parietal, rostral anterior cingulate and superior temporal regions ($0.009 < p < 0.049$). In the APOE ϵ 4 carriers, poorer memory performance was associated with less cortical thickness in ROIs showing reductions between groups.

Conclusions: The results suggest that cognitively normal late-middle-aged people with the major genetic risk factor for AD have decreased cortical thickness in brain regions known to be affected in AD and in healthy aging. MRI measures of cortical thickness may be helpful in detecting the earliest effects of AD on the brain. If these effects are found to progress over time, this method may assist efforts in evaluating prevention therapies for AD prior to the onset of cognitive impairment.

THE ROLE OF CATECHOL-O-METHYLTRANSFERASE AND DOPAMINE RECEPTOR D4 IN ADHD SYMPTOM VARIATION AMONG INDIVIDUALS WITH DOWN SYNDROME.

Mason GM, Edgin JO, Nadel L. University of Arizona; Arizona Alzheimer's Consortium.

Background: Individuals with Down syndrome (DS; Trisomy 21) have been shown to have difficulties in executive function, including the ability to acquire and implement new rules, inhibit responses, and maintain attention toward specific goals. Attention-deficit hyperactivity disorder (ADHD) is also associated with executive function deficits, and it is not uncommon for children with DS to exhibit ADHD symptoms. Genetics studies have indicated a relationship between variation in two prefrontal cortex genes, catechol-o-methyltransferase (*COMT*) and dopamine receptor D4 (*DRD4*), and differences in executive ability and ADHD symptom risk among typically-developing individuals. Our goal was to examine whether these genes also relate to the differences in executive function and ADHD symptoms in those with DS.

Methods: Participants included 77 individuals with DS (7-40 yrs) and 50 mental-age matched controls (3-6 yrs). Participants were tested using prefrontal measures taken from established assessments (e.g. CANTAB Eclipse, the Dots task). Additionally, caretakers completed questionnaires relating to ADHD symptoms. Genetics data was then analyzed for a subset of those with DS (n= 27, 7-20 yrs).

Results: Consistent with past research, individuals with DS showed executive difficulties and higher levels of inattention compared to controls. Within the DS subset, individuals carrying the *COMT val-val* genotype displayed more total omission errors on an attention task (CANTAB SRT), as well as more impairment on parent reports of working memory. Interestingly, those carrying the *COMT val-val* genotype also had fewer errors on a set-shifting executive function task (CANTAB ID/ED). While some trends were found for *DRD4*, greater sample size is needed before conclusions can be drawn.

Conclusions: Our results indicate that background genetics (genes not directly located on chromosome 21) can play an important role in phenotypic variation in Down syndrome.

As *COMT* is important for dopamine breakdown in the PFC, the results found for this gene suggest that dopamine regulation in the PFC has varying effects in DS depending on the particular executive function examined. For future research, it may be helpful to examine the strategy employed for the ID/ED set-shifting task to determine the patterns for the error differences observed between genotype. It will also be helpful to compare genotype/phenotype relationships between those with DS and controls to determine if the effects of background genes on these tasks are dampened or enhanced by trisomy 21.

Overall, this research adds to our knowledge of gene function under different developmental conditions, and may lead to better interventions and possible pharmacological treatments to assist those with DS.

DISTRIBUTED REGIONAL PATTERN OF GRAY MATTER VOLUME IN ALZHEIMER'S DISEASE: A COMPARISON WITH THE EFFECTS OF HEALTHY AGING. Menchola M, Bergfield KL, Hanson KD, Chen K, Lin L, Teipel SJ, Hampel H, Rapoport SI, Moeller JR, Alexander GE. University of Arizona; Banner Alzheimer's Institute, Banner Good Samaritan Medical Center; University of Rostock, Germany; University of Dublin, Ireland; Ludwig-Maximilian University, Germany; National Institutes on Aging; Columbia University; Arizona Alzheimer's Consortium.

Background: Alzheimer's disease (AD) is characterized by brain volume reductions on magnetic resonance imaging (MRI) with temporal and parietal regions most consistently and severely affected early in the clinical course. Healthy aging preferentially affects frontal regions, but reductions in other brain areas have been observed.

Methods: We investigated the relative effects of AD and healthy aging on MRI regional brain volume using voxel-based morphometry (VBM) with multivariate network analysis to first identify a regional pattern of MRI gray matter reductions in AD patients compared to healthy controls, and to subsequently test the ability of this pattern to distinguish the groups after we statistically controlled for aging effects using an age-related network pattern of MRI gray matter from an independent sample of healthy adults, 22 to 84 years of age. Ten otherwise healthy patients with possible or probable AD (mean age=65±9, M/F=6/4, mean Mini-Mental State Exam (MMSE)=16.1±6.3) and 15 age-matched healthy controls (mean age = 63±8, M/F=10/5, mean MMSE=29.5±0.7) were studied using volumetric T1 MRI scans with statistical parametric mapping (SPM5) VBM and customized tissue priors to produce gray matter volume maps.

Results: Multivariate network analysis with the Scaled Subprofile Model (SSM) identified a linear combination of two component patterns with higher expression in the AD patients than controls ($R^2=0.74$, $p<0.000001$). The combined pattern showed gray matter reductions in bilateral medial and lateral temporal and parietal areas, with relative preservation in cerebellum and anterior/mid cingulate regions. We then forward applied an age-associated network pattern of MRI gray matter to the AD and healthy control groups, which was derived from 29 healthy adults, 22 to 84 years of age using the same SPM5 SSM methods. The age-related pattern showed mainly bilateral reductions in medial and dorsolateral prefrontal, perisylvian, and precuneus regions, with relative preservation in thalamus. In a multiple regression model, expression of this age-related pattern was higher in the AD patients than controls ($R^2=0.24$, $p=0.013$). When subject scores for the AD-related pattern was added to the model, the additional 50% of the variance in distinguishing the groups was explained ($p<0.000002$) and the subject scores for the age-associated pattern were reduced to non-significance.

Conclusions: These results suggest that, despite prominent differences in the regional patterns of gray matter reductions, healthy aging and AD share some regional features of gray matter atrophy that may reflect underlying, developing disease in the context of healthy aging or exaggerated aging effects in AD dementia.

Poster 81

SMALL-ANIMAL PET/COLLIMATOR-LESS SPECT PROTOTYPING. Moore SK, Barrett HH, Furenlid LR. University of Arizona; Arizona Alzheimer's Consortium.

Background: Positron emission tomography (PET) imaging has become an important molecular imaging tool for biomedical research. In the Center for Gamma-Ray Imaging (CGRI) we have developed a novel PET prototyping platform that will allow testing and evaluation of multiple detector technologies for small-animal PET imaging. This platform can also be used as a high-sensitivity SPECT imager. This technique creates images without the use of collimation yielding a substantial increase in sensitivity. The high sensitivity of both techniques is especially applicable to studies in Alzheimer's disease in which incremental changes in plaque buildup are the only sign of the disease's progression.

Methods: The platform was designed using SolidWorks® and fabricated at CGRI. Using this platform we are evaluating different common low-cost monolithic NaI(Tl) modular cameras for using in small-animal PET imaging. We are also testing the importance of accurate depth of interaction estimation on the reconstructed image by using cameras with varied crystal thickness. Studies are also being performed testing the collimator-less SPECT modality.

Results: Preliminary PET reconstructions with a resolution phantom show a system resolution less than 2 mm. System detail and results will be shown.

THE EFFECTIVENESS OF MINDFULNESS-BASED STRESS REDUCTION AS AN INTERVENTION AMONG MIDDLE-AGED AND OLDER FAMILY CAREGIVERS OF PERSONS WITH NEUROCOGNITIVE DISORDERS. O'Donnell R, Kaszniak AW, Menchola M.
University of Arizona; Arizona Alzheimer's Consortium.

Objective: Providing care for a frail older adult is a stressful experience that may affect psychological and physical health of caregivers. When caregivers are elderly and the care recipient suffers from a neurocognitive disorder, such as dementia, the burden and resulting stress is greatly increased (Schulz, Martire, & Klinger, 2005).

Many interventions involving support groups, counseling, and education have been implemented to help caregivers. Interventions that actively engage the caregiver in skill acquisition aimed at regulating their own behavior have been shown to result in significant improvements in caregiver burden and depressive symptoms (Gitlin et al., 2003).

Methods: Mindfulness-Based Stress Reduction (MBSR) is an eight-week program that teaches people how to respond more effectively to stress, pain, and illness (Kabat-Zinn, 1990). The central focus of MBSR is intensive training in mindfulness meditation and its integration into the challenges of everyday life. Research has shown clinically relevant reductions in medical and psychological symptoms across a wide range of medical diagnoses, including chronic pain conditions and secondary diagnoses of anxiety disorders.

MBSR has not previously been studied with caregivers. The proposed study aims to ascertain whether MBSR is an effective intervention for a population of middle-aged and older family caregivers of persons with neurocognitive disorders by comparing it with a similarly structured intervention that focuses on Progressive Muscle Relaxation (PMR).

The specific questions this study will attempt to answer are:

1. Does MBSR decrease perceived levels of stress and depressive symptoms to a greater extent when compared to an active control condition?
2. Does MBSR increase perceived levels of mindfulness, self-compassion and general health status to a greater extent when compared to an active control condition?

Primary and secondary outcome measures will be used in analyses of within- and between-group changes from pre-intervention (baseline) to post-intervention, and at 8 weeks, 6 months and 1 year following the intervention.

Baseline to post-intervention results will be discussed in this poster in relation to prior studies of interventions with caregivers.

THE EFFECTS OF DISTRACTION AND INTERRUPTION FORMS OF INTERFERENCE ON DELAYED-NONMATCHING TO SAMPLE TASK PERFORMANCE. Plange K, Burke SN, Nematollahi S, Huerta D, Gazzaley A, Barnes CA. University of Arizona; University of California San Francisco; Arizona Alzheimer's Consortium.

Objectives: Memory performance is vulnerable to distracting stimuli, particularly, if the distracter requires attention and the human participants are older.

Methods: The current experiment adapted a task that has been used with humans to measure the effects of external interference factors on memory performance in nonhuman primates. The task was modified such that it could be used in a Wisconsin General Testing Apparatus. Monkeys learned to perform a trial-unique delayed-non-matching to sample task with a 30 sec delay period. All animals were required to reach a criterion performance of 90% over 5 consecutive days of testing. After animals reached this criterion, they participated in 5 days of testing in the “distraction” condition, in which irrelevant stimuli are presented and should be ignored during the delay period. During this condition the monkey was presented with a sample object that she was able to displace to obtain a food reward. A wooden guillotine door was closed for 10 sec, and then was raised, after which the monkey was presented with an irrelevant distracter that was behind a Plexiglas screen, so that the monkey could not touch the object. The wooden guillotine door was then lowered again for another 10 sec. Finally, the wooden door was raised and the monkey was presented with the sample object and a novel object. A correct trial occurred if the monkey displaced the novel object and obtained the food reward. After the distractor condition was complete, the monkeys participated in 5 days of testing in the “interruption” condition, in which a stimulus was presented that did require attention, but was not relevant to the final choice. The procedure for the interruption condition was similar to that of the distraction condition, except that the Plexiglas screen was not used and an irrelevant object was baited with a food reward that the monkey could retrieve by displacing the object.

Results: Overall, performance on the delayed-non-matching to sample task was not affected by the distraction condition, in which the interfering stimulus was irrelevant to obtaining food reward. In contrast, monkeys exhibited significantly more errors during the interruption condition, where the object, if attended, and displaced, could result in reward.

Conclusions: This suggests that, like humans, monkeys show disrupted memory performance in conditions in which interfering variables require attention.

UNDERSTANDING DIFFUSION-WEIGHTED MAGNETIC RESONANCE IMAGING VIA COMPUTATIONAL MODELING OF THE DIFFUSION OF WATER MAGNETIZATION.

Russell G, Secomb T, Harkins K, Trouard T. University of Arizona; Arizona Alzheimer's Consortium.

Objective: Diffusion-weighted MRI (DWMRI) is a powerful tool for quantitatively measuring the diffusion of water within living tissue. Because water diffusion is sensitive to the complex microscopic cellular environment, e.g. cell size, membrane permeability, white matter integrity, DWMRI is being applied to study a number of neurological disorders including Stroke, Cancer and Alzheimer's Disease (AD). However, understanding the biological and medical implications of DWMRI is not straight forward. The same complexity that gives DWMRI its clinical utility makes quantitative understanding of DWMRI data difficult. In order to extrapolate quantitative biological information from DWMRI, there is a need for more advanced analytical tools.

Methods: We have developed a time forward, center space, Finite Difference (FD) model of complex transverse magnetization concentration diffusion in biological tissue to be used for the analysis of DWMRI results. The numerical simulation we have developed can be used to predict experimental results and analyze data collected during DW-MRI experiments. Cellular size and geometries, intracellular and extracellular diffusion coefficients, intracellular and extracellular T2 relaxation times, and membrane permeability are all incorporated in our model. It extends previous work that required the short gradient pulse approximations to be assumed, an assumption that is rarely satisfied in clinical imaging. Using our new model in conjunction with DWMRI experiments will allow better understanding of the cellular changes and biophysical mechanisms underlying changes in water diffusion in response to disease. This deeper understanding, in turn, will lead to a better ability to diagnose, monitor, and treat neurological diseases such as AD.

AGE-RELATED DIFFERENCES IN WHITE MATTER DIFFUSION AND THEIR RELATION TO COGNITIVE FUNCTION ARE DETERMINED BY APOE STATUS. Ryan L, Walther K, Glisky EL. University of Arizona; Arizona Alzheimer's Consortium.

Background: There is growing evidence of an association between diminished cognitive function in healthy older adults and the apolipoprotein $\epsilon 4$ (APOE) allele, a major genetic risk factor for Alzheimer's disease (AD). This study assessed the relationship between age-related diffusion changes in white matter, cognitive functioning, and the presence of APOE $\epsilon 4$ in healthy older adults.

Methods: One hundred-twenty-six cognitively normal and healthy individuals (88 APOE $\epsilon 4$ noncarriers and 38 APOE $\epsilon 4$ carriers) ages of 52-92 underwent neuropsychological testing and were scanned on a GE 3T MRI scanner using an EPI Asset diffusion sequence with 2.6 mm sections covering the whole brain. Fractional anisotropy (FA) and the average diffusion coefficient (ADC) were determined using a region of interest analysis in frontal, temporal, and parietal regions, as well as the corpus callosum.

Results: ADC and FA diffusion measures changed with increasing age, replicating prior studies. Importantly, age-related differences in ADC and FA were significantly more pronounced in $\epsilon 4$ carriers than noncarriers across the whole brain, including frontal, temporal stem, and parietal white matter regions, as well as the genu, splenium, and the centrum semiovale. Regardless of APOE status, frontal diffusion measures predicted executive function scores. However, temporal lobe ADC predicted memory function for $\epsilon 4$ carriers, but not noncarriers.

Conclusions: The results suggest that APOE $\epsilon 4$ is associated with significantly greater age-related white matter differences, and that these differences predict both executive function and memory performance in healthy older adults.

SET-SHIFTING IN DOWN SYNDROME: COGNITIVE AND GENETIC CORRELATES. Spano G, Nadel L, Mason G, Edgin J. University of Arizona; Arizona Alzheimer's Consortium.

Background: Individuals with Down syndrome (DS) display impaired executive function (EF) due to abnormal development of the prefrontal cortex (PFC), including specific impairments on measures of set-shifting. One well-established set-shifting task is the Dimensional Change Card Sorting (DCCS) task. In this task subjects sort cards based on one dimension (color) and then shift to sorting by the other dimension (shape).

Methods: The present study uses modified versions of the DCCS to test whether or not EF deficits will persist when representational demands are lessened. Also, in order to better understand the cognitive components underlying set-shifting deficits in DS, we compared this task to a task measuring working memory and inhibitory control. Given the evidence for a correlation between Catechol-O-methyltransferase (COMT) allelic variation and PFC performance, we investigated whether the DS groups' performance on EF tasks could also be partly explained by variation in COMT. Children and adolescents (n=26, ages 8-24) with DS were matched to a control group of 26 typically developing children on the basis of mental age.

Results: Results showed that individuals with DS failed to switch sorting dimensions in all conditions, as compared to controls. Moreover, when DCCS performance was worse, they had more difficulty learning the task demands and shifting between rules. Furthermore, DCCS deficits appear to relate to verbal WM. Finally, DCCS performance was related to COMT, suggesting that the background level of dopamine plays a role in these deficits in DS.

Conclusions: Our results suggest that impairments in executive function, in particular set-shifting, is a feature of DS. The presence of a deficit on this measure seems to relate to polymorphisms of COMT affecting prefrontal function.

LONGITUDINAL CHANGES IN MEMORY AND EXECUTIVE FUNCTIONING IN COGNITIVELY HEALTHY APOE E4 CARRIERS. Walther K, Glisky EL, Ryan L. University of Arizona; Arizona Alzheimer's Consortium.

Background: There is growing evidence of an association between diminished cognitive function in healthy older adults and the apolipoprotein $\epsilon 4$ (APOE) allele, a major genetic risk factor for Alzheimer's disease (AD).

Methods: The study examined changes in memory and executive functioning in cognitively healthy older adults over a 2-4 year time period. Thirty-six APOE $\epsilon 4$ non-carriers and 20 APOE $\epsilon 4$ carriers (ages 50–83) underwent neuropsychological testing at two time points (26-46 months between tests).

Results: All participants performed in the normal range during the first testing. Repeated measures ANOVA controlled for age at Time 1 and time between testing were performed on two composite scores, memory and executive function. A significant interaction between Time and APOE status was observed for executive functioning ($p < .05$). While both groups performed similarly at Time 1, APOE $\epsilon 4$ carriers showed a stronger decline in executive functioning compared to controls at Time 2. Memory performance also showed a significant Time by APOE status interaction ($p < .01$). Whereas memory performance increased for noncarriers, possibly reflecting retest effects, memory performance remained stable in APOE $\epsilon 4$ carriers.

Conclusions: The results suggest a faster decline in cognitive function, particularly executive functioning, in carriers of the APOE $\epsilon 4$ allele over a period of 2-4 years. It remains unclear as to whether the decline in cognitive performance reflects preclinical symptoms of AD or whether the presence of the APOE $\epsilon 4$ allele accelerates the process of normal aging.

WHITE MATTER INTEGRITY IS ALTERED WITH INCREASED BODY WEIGHT IN OLDER FEMALES. Walther K, Ryan L. University of Arizona; Arizona Alzheimer's Consortium.

Background: In a recent study examining the relationship between Body Mass Index (BMI), cognition, and differences in brain volume in a sample of 95 community-dwelling older females (ages 52 – 92; BMI range 18.5 – 45), higher BMI was associated with decreased executive functioning and regions of decreased gray matter volumes in frontal, temporal, parietal, and cerebellar regions. In addition, *increased* volumes of white matter were observed in the same regions (Walther et al., HBM, in press). It remains unclear whether these increases reflect healthy expansion of myelin or damaged white matter.

Methods: To address this question, diffusion MRI was used to assess the integrity of white matter in the same sample of older females within the same regions of white matter showing BMI-related increases in volume. Diffusion images were acquired on a 3T GE scanner using an echo planar sequence covering the whole brain and measures of fractional anisotropy (FA), axial diffusion, and radial diffusion were extracted.

Results: Results indicate a pattern of changes that suggest damage to these regions. After controlling for age, BMI was negatively correlated with FA bilaterally in the temporal white matter. Axial diffusivity also decreased with higher BMI in the right frontal and the left temporal stem white matter. Finally, radial diffusivity was positively correlated with BMI in the temporal and parietotemporal white matter.

Conclusions: The results suggest that increased white matter volumes observed with increasing body weight do not result from increases in normal myelin density, but instead reflect pathology that may include damage to the myelin sheath, increased oedema, or both.

ULTRA-SHORT TE IMAGING IN ALZHEIMER'S DISEASE. Yoshimaru E, totenhagen J, Trouard T. University of Arizona; Arizona Alzheimer's Consortium.

Background: Magnetic Resonance Imaging (MRI) is a medical imaging technique recognized for its ability to noninvasively view soft tissues of the body without the dangers of ionizing radiation. Our interest lies in developing new MRI techniques to image biomarkers associated with neurological diseases such as Alzheimer's disease (AD). In previous experiments [1,2], investigators have used high-resolution T2-weighted imaging to identify the presence of amyloid- β (A β) deposits in the brains of Alzheimer's mice. A β plaques are thought to contribute to the progression of AD disease and are a therapeutic target for drugs being developed to prevent, arrest, or reverse the disease. In the T2 weighted imaging, signal dropouts were observed that correlated to the presence of plaque as assessed on histological staining.