ultra-sensitive and specific mass spectrometry assay for ATIP. Using a technique that permits targeted analysis of multiple peptides across multiple samples in a single mass spectrometry run, known as TOMAHQAQ, we have identified specific human tryptic peptides that permit quantification of ATIP abundance. We have used this method to quantify ATIP in postmortem frontal cortex samples of older adults (n=60) with Alzheimer’s dementia (AD). We correlated levels of ATIP to brain RAS receptors, and biomarkers of AD pathogenesis including oxidative stress, inflammation, mitochondrial dysfunction as well as amyloid-β, and tau burden. Our results show that ATIP expression (ANLKNPQIMYLEQELESLK sequence of ATIP) is positively correlated with neuronal nitric oxide synthase (nNOS) (p = 0.009, r = 0.337). Furthermore, expression of ATIP is negatively correlated with amyloid-β load in several brain regions including hippocampus (p= 0.014, r=-0.317), entorhinal cortex (p= 0.010, r=-0.331), frontal cortex (p= 0.023, r=-0.294), and overall (p= 0.004, r=-0.365). These results highlight a potential protective role for ATIP in Alzheimer’s disease.

IS CEREBRAL AMYLOID ANGIOPATHY A PRECIPITATING EVENT IN THE ETIOLOGY OF ALZHEIMER’S DISEASE

Steven Edland1, Chris Zarow1, Benjamin Shifflett2, Margaret Flanagan1, and Lon White1. 1. University of California, San Diego, San Diego, California, United States, 2. University of California, San Diego, La Jolla, California, United States, 3. Northwestern University, Evanston, Illinois, United States, 4. Pacific Health Research and Education Institute, Honolulu, Hawaii, United States

Amyloid plaque and cerebral amyloid angiopathy (CAA) are early neuropathologic changes observed in the setting of classical Alzheimer’s disease (AD), typically preceding biomarker evidence of intraneuronal tau neurofibrillary tangle (NFT) development and associated cognitive decline. Here we apply structural equation models to explore the potential causal associations between amyloid-beta lesions (i.e. plaques and CAA) and NFTs as they affect cognitive performance in the elderly. Brain autopsy data used in this study are from the Honolulu Asia Aging Study (HAAS) of Japanese American men from the state of Hawaii (n=600), and the Nuns Study (NS) of Roman Catholic Sisters largely from the upper midwestern United States (n=378). Cognitive performance within three years of death was assessed by multi-domain dementia rating scales. We found that neocortical neuritic plaque and CAA effects on cognitive performance were mediated by neocortical NFTs for both the HAAS (p < 0.002) and NS (p < 0.043). There were no direct effects of neuritic plaque and CAA after controlling for the mediating effect of NFTs (p > 0.54). These data are consistent with the hypothesis that the association between neuritic plaque and CAA on cognition is mediated by NFT load. This may inform our understanding of the etiology of NFT lesion pathology in aging and AD. The disruption of arterial smooth muscle function by CAA has predictable effects on lymphatic processes and on the regulation of capillary blood flow. These effects are plausibly relevant to the AD neurodegenerative process, and these pathways deserves continued attention by the AD research community.

DETECTION OF PRECLINICAL AND PRODROMAL ALZHEIMER’S DISEASE USING A MULTIDISEASE DIAGNOSTIC PLATFORM

Cassandra DeMarshall1, Jeffrey Viviano1, Sheina Emrani2, George Godsey3, Abhirup Sarkar3, Benjamin Belinka1, David Libon2, and Robert Nagele2. 1. Durin Technologies Inc., Mullica Hill, New Jersey, United States, 2. Durin Technologies Inc., Mullica Hill, New Jersey, United States, 2. Rowan University School of Osteopathic Medicine, Stratford, New Jersey, United States

AD-related pathological changes begin in the brain long before symptoms emerge. In the present study, we demonstrate the utility of a panel of AD-related autoantibodies capable of detecting AD at the earliest points along the AD continuum, including preclinical AD, years before the onset of symptoms, and prodromal AD (mild cognitive impairment, MCI). Using a customized panel of AD-specific autoantibody biomarkers and Luminex xMAP® technology, sera from ADNI subjects with preclinical AD or MCI were screened to demonstrate preclinical and prodromal AD detection. A panel of eight autoantibodies with increased titer in MCI and preclinical AD relative to controls was evaluated using Random Forest and Receiver Characteristic Operating curves for their ability to distinguish diseased subjects from age- and sex-matched controls, as well as from individuals with other neurodegenerative and non-neurodegenerative diseases. Results showed that this panel of biomarkers was capable of differentiating patients with MCI from age- and sex-matched controls with high overall accuracy, sensitivity, and specificity. These biomarkers also identified cognitively normal subjects who later converted to MCI and AD. Furthermore, this autoantibody biomarker panel distinguished MCI and preclinical AD subjects from Parkinson’s disease and breast cancer subjects, demonstrating excellent disease specificity. Results demonstrate the utility of our blood-based autoantibody biomarker panel as an accurate, non-invasive, and inexpensive diagnostic screener, not only for the detection of prodromal AD, but also the earlier, preclinical stages of AD pathology. This multi-disease diagnostic platform has been demonstrated to be useful for multiple neurodegenerative diseases including AD, Parkinson’s disease and Multiple Sclerosis.

INTEGRATIVE MULTI-OMICS ANALYSIS REVEALS THE CRITICAL ROLE OF PBXIP1 GENE IN AGING-RELATED ALZHEIMER’S DISEASE

Zuyun Liu, Jingyun Zhang, and Xiaoyi Sun, Zhejiang University School of Medicine, Hangzhou, Zhejiang, China (People’s Republic)

Alzheimer’s disease (AD) is a neurodegenerative disorder, and its strongest risk factor is aging. A few studies have explored the relationship between aging and AD, while the underlying mechanism remains unclear. We assembled data cross multi-omics (i.e., epigenetics, transcriptomics,
and proteomics, based on frozen tissues from the dorsolateral prefrontal cortex and neuropathological and clinical traits from the Religious Orders Study and Rush Memory and Aging Project (ROSMAP). Aging was assessed using six epigenetic clocks (including Horvath clock, Hannum clock, Levine clock, Horvathskin clock, Lin clock, and Cortical clock) that capture mortality risk in literature. After accounting for age, we first identified a gene module (including 263 genes) that was related to most epigenetic clocks (e.g., $P=3.61 \times 10^{-5}$ for Levine clock) and three neuropathological traits of AD (i.e., β-amyloid, Tau tangles, and tangle density). Interestingly, among 20 key genes with top intramodular connectivity of the module, PBXIP1 was the only one that was significantly associated with all three neuropathological traits of AD at the protein level after Bonferroni correction. Furthermore, PBXIP1 was associated with clinical diagnosis of AD in both ROSMAP and two independent datasets. The results suggest the critical role of PBXIP1 in aging-related AD and support the potential and feasibility of using multi-omics data to investigate mechanisms of complex diseases. However, more validations in different populations and experiments in vitro and in vivo are required in the future.

**LOCI RESPONSIBLE FOR RACIAL DISPARITY BETWEEN WHITE AND BLACK AMERICANS IN ALZHEIMER’S DISEASE**

Stanislav Kolpakov Nikitin, and Igor Akushevich, Duke University, Durham, North Carolina, United States

We tested the following genotype-related mechanisms generating race-dependent disparity in Alzheimer’s Disease (AD) risk: i) the frequencies of SNPs with genotypes associated with AD are higher in the Black subpopulation; ii) the effects on AD risk of genotypes associated with increased AD risk is higher in the Black subpopulation; iii) there is a small group of SNPs with a large difference in the effects on AD race-dependent risk generating disparities; alternatively, the disparities are generated by a collective effect of multiple SNPs with minor or moderate effects. We modified the GWAS algorithm to use it with the Cox regression multivariable model and the outcome accounting for race-related differences in AD risk. Using the modified GWAS we have identified loci in charge for the disparity between Whites and Blacks and used the results along with SNPs of a special interest which were identified from the literature in the Cox multivariable regression model and generalized Oaxaca-Blinder approach. The following genes had the strongest effects on racial disparities: i) NYAP1 neuronal tyrosine-phosphorylated phosphoinositide-3-kinase adaptor; ii) RPA3-UMAD1 loci RPA3 replicates protein A, interacting with gastric tumor and hepatocellular carcinoma; iii) TOMM40 associated with an increased risk of developing late-onset AD; iv) ACE - responsible for making the enzyme which converts angiotensin which regulates blood pressure; v) PSME3IP1 - proteasome activator subunit 3 interacting protein 1; vi) MARCHF1 regulator of glucose-tolerance and lipid storage and vii) LINCO1146 which belongs to coagulation cascade pathway and linked to hepatocellular carcinoma.

**A NOVEL FRAMEWORK LINKING MNEMONIC AND HIPPOCAMPAL INTEGRATION TO LATE-LIFE REAPPRAISAL EFFICACY**

Bruna Martins-Klein1, Irina Orlovsky2, and Kristin Heideman3, 1. University of Southern California, Los Angeles, California, United States, 2. University of Massachusetts Amherst, Amherst, Massachusetts, United States, 3. Yale Child Study Center, New Haven, Connecticut, United States

Socioemotional theories suggest that surviving challenging experiences enhances emotional resilience with age, yet the role of memories is overlooked in most models of emotion regulation. In parallel, cognitive accounts focus on age-related memory deficits associated with overlapping hippocampal neural representations across unique memories (neural dedifferentiation). We propose a novel framework supporting enhanced late-life reappraisal via hippocampal dedifferentiation of memory representations across current and past experiences. We review classic studies supporting mood benefits from integrated positive narratives following adverse autobiographical events. We also discuss multivariate neuroimaging evidence supporting overlapping hippocampal representations and ventromedial prefrontal cortex (vmPFC) involvement in meaning-making processes. We posit that greater hippocampal dedifferentiation across life memories may facilitate associative binding of current and past stressors as well as reappraisals in vmPFC. This process may provide avenues for generalizing past reappraisals to novel contexts and reducing cognitive demands of reappraisal. In addition, we discuss the possible age-related facilitation of this process, as a greater number of life experiences may become increasingly integrated with one another over the lifespan. These integrated neural associations may serve to make reappraisals from the past more readily accessible and applicable in new contexts over time, increasing routes to positive narratives following stress. We discuss future directions for testing components of the proposed model using multivariate neuroimaging methods. We conclude by briefly reviewing the possible clinical impact of mnemonic emotion regulation in promoting emotional well-being among older adults, using a strengths-based approach that leverages wisdom from experience and neural processes facilitated with age.

**SPATIALLY RESOLVED MAPPING OF CELL-SPECIFIC SENESCENT PROFILES IN AGING MOUSE BRAIN**

Chase Carver, and Marissa Schafer, Mayo Clinic, Rochester, Minnesota, United States

Cellular senescence is a conserved mechanism of aging characterized by cell cycle arrest and secretion of a senescence-associated secretory phenotype comprised of proinflammatory cytokines, chemokines, proteases, and growth factors that disrupt cellular homeostasis by promoting sterile inflammation and aberrant tissue remodeling. Tissue microenvironment, induction mechanism, and duration since senescence onset contribute to senescent cell heterogeneity, making identification challenging. Senescent cell contribution to age-related cognitive decline suggests that the hippocampus may be a key brain region for uncovering