

Session 9055 (Poster)

Alzheimer's Disease and the Brain

AGE-ASSOCIATED EPIGENETIC ALTERATIONS, SOMATIC MUTATIONS, AND THEIR CROSSTALK IN ALZHEIMER'S DISEASE

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Aging is the major risk factor for Alzheimer's Disease (AD), and as life expectancy increases, neurodegeneration will continue to afflict an ever-increasing proportion of the population. While numerous theories are attempting to explain the drivers behind AD pathology, what unites them is the observation that AD is reliably associated with a progressive buildup of age-related molecular changes. Because of the varying clinical presentations of AD in patients with similar genetic backgrounds, it has been postulated that epigenetics may be implicated in its etiology. Building on our prior work showing that AD pathology is linked to alterations in age-related DNA CpG methylation (DNAm) across various brain regions, we use state-of-the-art machine learning approaches to identify patterns of molecular damage in postmortem brain samples. We show that alterations in DNAm are associated with accelerated biological aging, AD, and the APOE e4 genotype, which is a major risk factor for AD. We also demonstrate that these associations are present in the PFC but not cerebellum -- in line with the current understanding of AD progression in the brain. Finally, we perform whole-exome sequencing and protein mass spectrometry on the same brain samples to test our hypothesis as to whether AD-associated alterations of DNAm are linked with the accumulation of somatic mutations that affect the structural and binding properties of protein epigenetic regulators.

ANGIOTENSIN RECEPTOR BLOCKERS UPREGULATE ANGIOTENSIN TYPE 4 RECEPTOR IN BRAINS OF COGNITIVELY INTACT INDIVIDUALS

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The primary dementia-protective benefits of Angiotensin receptor type 1 (AT1R) blockers (ARBs) are believed to arise from systemic effects on blood pressure. However, there is a brain-specific renin-angiotensin system (b-RAS) that acts mainly through three receptor subtypes: AT1R, AT2R, and AT4R. AT1R promotes inflammation and oxidative stress (OS). AT2R increases nitric oxide. AT4R is essential for dopamine release and mediates memory consolidation. Here, we aimed to investigate the effects of ARBs on b-RAS, OS, inflammation, PHF-tau, and beta-amyloid load. Postmortem frontal-cortex brains of age- and sex-matched cognitively

intact (CI) individuals using (n=30) and not using ARBs (n=30) and Alzheimer's disease (AD) patients using (n=30) and not using ARBs (n=30) were studied. Protein levels of receptors were measured by Western blot. Protein carbonyl (PC) and cytokine levels were measured by ELISA. Tangle and amyloid- β scores were used as outcomes. In CI individuals, our data shows that ARB treatment was associated with higher protein levels of AT4R (median(range) 0.69(1.92) vs 0.17(1.18) CI+ARBs vs CI, $p=0.02$), lower level of OS marker PC (10.60(8.32) vs 11.26(7.44), CI+ARBs vs CI, $p=0.03$) and lower hippocampal and overall amyloid scores (0(5.45) vs 1.15(4.21) $p=0.03$, 0.79(12.75) vs 3.41(13.36) $p=0.04$, CI+ARBs vs CI, respectively). In AD group, ARB treatment was associated with lower AT1R protein levels (0.47(1.15) vs 0.59(1.99), AD+ARBs vs AD, $p=0.02$). No significant changes were observed in OS, inflammation, or PHF-tau and amyloid load in AD brains treated with ARBs. Our results highlight the impact of ARBs on the brains of cognitively intact and AD older individuals.

COMPARING CORTICAL DEMYELINATION IN GERIATRIC MILD TRAUMATIC BRAIN INJURY AND ALZHEIMER'S DISEASE

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Mild traumatic brain injury (mTBI) accelerates the rate of age-associated brain atrophy, whose pattern resembles the cortical neurodegeneration pattern observed in Alzheimer's disease (AD). Because the ratio R of T1-to-T2-weighted magnetic resonance imaging (MRI) intensities is a surrogate measure of cortical myelin concentration, mapping and quantifying changes in this ratio can improve our understanding of demyelination after geriatric mTBI and AD. T1- and T2-weighted MRIs were acquired acutely and ~6 months post-injury from 68 healthy controls (HCs, age (years, y): $\mu = 76$ y, $\sigma = 4$ y), 19 mTBIs (age $\mu = 70$ y, $\sigma = 5$ y), and 33 ADs (age $\mu = 77$, $\sigma = 6$). Volumes were co-registered using 3D Slicer's BRAINSFit module, and T2-constrained segmentations of T1 volumes were obtained using FreeSurfer. R and its time changes were computed at each cortical location. When comparing mTBI and AD patients to HCs, significant differences in R were found across ~10% and ~23% of the cortex, respectively ($p < 0.05$). When comparing mTBI to AD, the former exhibited significantly less myelin content in the lateral, medial, and ventral temporal lobes ($p < 0.05$), on the medial aspects of superior parietal lobules and superior frontal gyri ($p < 0.05$), and in orbital gyri ($p < 0.05$), whereas AD subjects had less myelin content on lateral aspect of the parietal lobe ($p < 0.05$). These results highlight demyelination differences in mTBI and AD. Future studies should examine the long-term trajectories to quantify the risk of neurodegenerative disease after mTBI.

DECOUPLING OF GLOBAL BRAIN ACTIVITY AND CEREBROSPINAL FLUID FLOW IS LINKED TO ALZHEIMER'S PATHOLOGY

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