respectively]. Both positive behaviors and higher age 20 GCA were associated with less brain aging. The GCA-lifestyle interaction was also significant. Those with both lower age 20 GCA and fewer positive behaviors had older brains relative to chronological age [F=5.00; p=. 03]. When GCA was high, however, participants had younger brains, regardless of lifestyle behaviors, suggesting a protective effect of early high GCA or cognitive reserve on later brain health. However, for those with lower cognitive reserve, positive lifestyle behaviors appeared to be protective against brain aging nearly three decades later. Results highlight the important role of cognitive reserve and lifestyle factors for later life brain health.

AGING RELATED TRANSCRIPTOMIC CHANGES IN THE MOUSE MODELS OF ALZHEIMER'S DISEASE

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Alzheimer's Disease (AD) is characterized by multiple clinical phenotypes and molecular signatures at different stages of the disease and aging is the major risk factor for sporadic AD. Aging and AD are linked at molecular, cellular and systems level with commonalities in inflammation and associated immune response in the brain. Mouse models of AD were developed that mimic various aspects of aging-associated neurodegeneration and inflammation. Research in mouse models of AD showed that drugs and treatments designed for AD can decelerate aging phenotypes suggesting efficient utilization of these models in aging research. We analyzed RNA-Seq transcriptomic data from transgenic mouse models of familial AD (APP/PS1 and 5XFAD) and knock-in mouse models of late-onset AD (APOE and TREM2) at the ages between 4-months and 24-months. The number of differentially expressed genes between transgenic/knock-in and WT mice increased by age in all mouse models. Gene set enrichment analysis identified metabolic pathways, including oxidative phosphorylation, altered in an age and genotype related manner in the brain of APP/PS1 and 5XFAD mice that recapitulate major features of amyloid pathology. Immunity related pathways were enriched in APOE4 model carrying Trem2*R47H mutation at >12 months-old. We also mapped the transcriptional signatures to co-expression gene modules of human LOAD from the AMP-AD consortium and observed correlations specific to each mouse model. Our study provides a detailed view of how the aging interacts with AD-relevant pathologies at the transcriptome level and demonstrates potential translational relevance of the AD mouse models in the context of human aging.

ALZHEIMER'S DISEASE-ASSOCIATED PATHOLOGY IN A TRANSGENIC MOUSE MODEL RESULTS IN ALTERED VOIDING FUNCTION

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Alzheimer's disease (AD) is a devastating disorder primarily affecting older adults and is the most common neurodegenerative disease in the US. More than one in three AD patients experience AD-associated urinary dysfunction (ADUD), which directly contributes to their institutionalization. While ADUD has been clinically regarded as a result of poor cognitive control over urinary function, the physiology underlying loss of urinary control remains unknown. We hypothesize that beta-amyloidosis in the CNS results in pathologic changes in urinary structure and function. Male and female Tg-APP/PS1DE9 mice were used before plaque deposition (4-6 months) and after plaque accumulation (8-10 months) and compared to their WT littermates. Pressure-flow cystometry was conducted under urethane anesthesia to assess urinary performance at the level of the autonomic nervous system in the absence of cortical control. Pharmacomyography was performed on bladder strips to determine tissue-level changes in the absence of CNS input. In Tg-APP/PS1DE9 mice, plaque accumulation resulted in diminished volume sensitivity and decreased voiding efficiency. Pharmacologic studies showed aberrant drug responses, altered cholinergic signaling, and decreased resilience of tissue longevity after plaque accumulation. Based on our findings, we conclude that the AD-related pathology of Aβ accumulation results in a distinct urinary phenotype in our model, analogous to the ADUD observed in AD patients. Establishing and expanding models of ADUD to other mouse models of AD-associated pathology may improve the efficacy of treating ADUD and increase quality of life for patients and their caregivers.

CAROTID REVASCULARIZATION IMPROVES BALANCE AND MOBILITY, PARTICULARLY IN PATIENTS THAT ARE MOST IMPAIRED

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Balance and mobility function worsen with age, and more so for those with underlying diseases. Our research has demonstrated that asymptomatic carotid artery stenosis (ACAS) is associated with worse balance and mobility, and a higher fall risk, compared to older adults with similar comorbidities, but without ACAS. Thus, ACAS, with attendant blood flow-restriction to the brain is a potentially modifiable risk factor for balance and mobility dysfunction. The purpose of this study was to evaluate the impact of restoring blood flow to the brain by carotid revascularization, on balance and mobility in patients with high-grade ACAS (≥70% diameter-reducing stenosis). Twenty adults (67.0±9.4 years) undergoing carotid revascularization for high-grade stenosis were enrolled. A balance and mobility assessment was performed before- and six weeks- after carotid revascularization and included: Short Physical Performance Battery (SPPB), Berg Balance Scale (BBS), Four Square Step Test (FSST), Dynamic Gait Index (DGI) Timed Up and Go (TUG), gait speed, MiniBESTest, and Walk While Talk (WWT) test. Paired t-tests assessed changes in outcome measures between the two-time points. Significant improvements were observed in measures that combined walking with dynamic movements, DGI (P=0.003), and MiniBESTest

(P=0.021). Pearson's correlations examined the relationship between balance and mobility before surgery and change score after surgery. Patients with lower baseline DGI and MiniBest scores demonstrated the most improvement on follow-up testing (r=-0.70, p=0.001, and r=-0.59, p=0.006, respectively). In conclusion, revascularization of a carotid artery stenosis improves balance and mobility; the greatest improvements are observed in those patients that are the most impaired.

COGNITIVELY IMPAIRED OLD MICE DISPLAY CORRELATED REDUCTION IN CORTICAL NMDA RECEPTOR AND COMPLEX IV

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Cognitive decline in older adults represents a major challenge since cognitive impairment is found in 10% of those ≥ 65 and 50% ≥ 85. Thus it is increasingly important to understand the impact of aging on cognitive health. We performed a battery of tests to assess cognition in 6 month-old (n=12) and 24 month-old (n=8) C57BL/6J mice, equivalent to 30 and 70 year old humans, respectively, and also assessed protein markers in cortex for mitochondrial health and cognition. We found that aged mice displayed fewer spontaneous alternations in the T maze test (p=0.034) and lower recognition of novel objects (p=0.022). In addition, aged mice showed prolonged escape time in the Barnes maze (p=0.035), all of which taken together suggest reduced capacity for learning and recall. Aged mice also exhibited diminished nest building (p<0.001), revealing an impaired functional capacity analogous to the instrumental activities of daily living (IADL) geriatric assessment. We found reduced mitochondrial complex IV expression in the cortices of aged mice concomitant with less expression of N-Methyl D-Aspartate (NMDA) receptor subunits 1, 2A and 2B. The cortices from old mice also exhibited greater expression of immature brain derived neurotrophic factor (pro-BDNF). The alterations in NMDA receptors and pro BDNF are consistent with memory impairment and greater neuronal cell death. Therefore, aged mice exhibit significantly reduced recall and learning ability alongside marked alterations in mitochondrial complex, NMDA receptor, and pro-BDNF expression. Studies are underway to assess whether these molecular changes are responsible for the cognitive declines with aging.

CO-OCCURRENCE OF PHYSICAL AND COGNITIVE DECLINE IN VERVET MONKEYS (CHLOROCEBUS AETHIOPS SABAEUS)

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Age-related neurodegeneration associated with Alzheimer's (AD) disease begins in middle age, well before the onset of symptoms. Therefore, translational models to identify modifiable risk factors in middle-age are needed to understand etiology and identify therapeutic targets. Vervet monkeys (Chlorocebus aethiops sabaeus), like humans, naturally develop several risk factors for AD with age, including obesity, prediabetes, and hypertension. Furthermore, older vervets exhibit accumulation of amyloid and tauopathies, decreased brain volumes, and physical declines in gait speed, suggesting that these NHPs may be useful models of early AD-like neuropathology. Currently, we are investigating the extent to which cognitive and physical decline co-occur in 20 elder (mean age=23 years, ~equivalent to a human age of 80 years) and 10 middle-aged (mean age=11 years) females through assessments of physical performance, executive function, social cognition, and short-term memory. These measures are part of a larger study to integrate physical, social, and cognitive function with measures of body composition, metabolic profiles, CSF, blood, neuroimages, and neuropathology. While tests of social cognition and short-term memory are ongoing, assessments of executive function indicate that performance declines with age (N=26; p<0.05; R-squared=0.23). Furthermore, animals that exhibit slower gait speed also perform poorly on the executive function task (N=26, p<0.05; R-squared=0.25). These preliminary results suggest that accelerated aging co-occurs in multiple systems in vervets. This study will enable examination of temporal relationships between physical and cognitive declines. Ultimately, this comprehensive, integrative whole-body approach will help clarify the mechanisms underlying divergent aging trajectories and inspire interventions that promote multi-system healthy aging.

DETERMINING THE ROLE OF APOE4 IN AGE-RELATED CEREBROVASCULAR DECLINE

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Cerebrovascular decline occurs during aging and may be critical during prodromal phases of Alzheimer's disease (AD). The E4 allele of apolipoprotein E (APOE4) is the greatest genetic risk factor for AD and decreased longevity and studies suggest APOE4 increases risk for age-dependent cerebrovascular damage. To study the relationship between APOE4 and age-related cerebrovascular decline, male and female C57BL/6J (B6) mice carrying combinations of APOE alleles including APOE4 (risk) and APOE3 (neutral), as well as B6 controls were assessed at a variety of ages from 4 to 24 mos for cognitive ability, biometrics and cerebrovascular health including i) PET/MRI using 64Cu-PTSM (perfusion) and 18F-FDG (metabolism), ii) transcriptional profiling and iii) immunofluorescence. Despite no cognitive decline, male APOE4 mice showed hypo-perfusion and hypo-metabolism by 12 mos, while female APOE4 mice showed an uncoupled hyper-perfusion and hypo-metabolism phenotype. Transcriptional profiling showed differential expression of genes involved in regulation of cerebral perfusion, glucose transportation and metabolism in APOE4 mice. An age-dependent blood brain barrier compromise was also apparent in the brains of female APOE4 mice. Physical activity reduces risk for human AD and our data shows exercise