cardiovascular (Diastolic Blood Pressure, Systolic Blood Pressure, pulse rate), metabolic (Total Cholesterol, HDL cholesterol, Triglycerides, Glucose, Body Mass Index) and inflammation markers (Albumin, White Blood Count) with Post-traumatic Stress Disorder (PTSD), cognitive functioning (Montreal Cognitive Assessment) and frailty (Short Physical Performance Battery) in responders from the World Trade Center (WTC). We first examined correlations between biomarkers, PTSD symptom severity, PTSD dimensions, cognitive functioning and frailty. We then conducted multivariate regression analyses. In models adjusted for potential confounders, among N=1,045 responders, elevated PTSD was strongly associated with increased frailty, cardiovascular dysregulation and mild cognitive impairment. Current work is ongoing to identify trajectories of change in cognition with frailty and biological factors.

PARASYMPATHETIC INFLUENCE ON COGNITIVE AGING IS MODERATED BY SYMPATHETIC ACTIVITY, ESPECIALLY IN EARLY MIDLIFE

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The two branches of the autonomic nervous system (ANS) have been individually linked to age-related changes in cognitive functioning: The parasympathetic nervous system (PNS) is thought to support healthy cognitive aging, whereas the sympathetic nervous system (SNS) has been linked to heightened cognitive decline. Despite these separate findings and despite the integrative nature of the ANS, little work has examined the two branches simultaneously to better understand their interactive effects on age-related cognitive changes. We examined cognitive change in two waves of the MIDUS cognitive project and indexed PNS and SNS activity from heart rate variability and epinephrine levels (respectively) from the MIDUS biomarker project (n = 764, 56% female, mean age = 54.1 years). Our findings indicate that higher PNS levels attenuate cognitive decline, but only among individuals with low SNS levels; at higher SNS levels, the beneficial effects of the PNS are blocked. Further, lower PNS levels can be somewhat compensated for by increased SNS levels. This pattern was most robust among individuals transitioning to mid-life (i.e., 35-40 years old at the initial cognitive test). These results suggest that interventions targeting the ANS as a modifiable factor in cognitive aging should consider both ANS branch's effects simultaneously, particularly in the early stages of midlife.

MTOR-DRIVEN ALTERATIONS IN THE BRAIN MICROVASCULAR PROTEOME IN ALZHEIMER'S DISEASE

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Therapeutic interventions for Alzheimer's disease (AD) remain limited due to an incomplete understanding of the molecular mechanisms of its onset and progression. Cerebrovascular dysfunction occurs early during disease development. Attenuation of mTOR, a key regulator of aging, attenuates and reverses cerebrovascular deficits by restoring cerebral blood flow, brain vascular density, neurovascular coupling, and vascular amyloid-β clearance in hAPP(J20) mice expressing human amyloid precursor protein carrying two FAD-associated mutations. The mechanisms by which mTOR attenuation alleviates AD pathology are poorly understood. This study defined changes in the microvascular proteome of hAPP(J20) mice arising from mTOR attenuation. At 7 months of age, hAPP(J20) mice were fed vehicle- or rapamycin-supplemented diet (2.24 mg/kg/day) for 4 months. Mass spectrometry of collected brain microvasculature identified significant changes in 840 of 3361 proteins ($p<0.05$). mTOR attenuation led to significant changes in 26 of these proteins, some of which are involved in pathways including tight junction regulation, calcium signaling, and actin cytoskeleton regulation. Candidate mediators of mTOR-driven cerebrovascular dysfunction were identified by selecting proteins that were aberrantly altered in hAPP(J20) microvasculature and normalized by rapamycin. Examples include members of the heterogeneous nuclear ribonucleoprotein family (hnRNPA/B, hnRNPD) which regulate the mRNA stability of genes related to cellular cycle arrest and inflammatory cytokines as well as localization of crucial mRNA involved in nitric oxide signaling. Also included are nucleoporin 54 and vacuolar ATPase assembly factor, both of which are altered in aging and neurodegeneration. Subsequent studies will elucidate the role of these proteins in mTOR-driven cerebrovascular dysfunction in AD.

A GENERIC METHODOLOGY FOR EFFECTIVE CREATION OF LABORATORY-TEST-BASED FRAILTY INDICES

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Laboratory test-based frailty indices (FI) are known to be highly predictive of adverse health outcomes and mortality. However, these FI depend on the proper classification of continuous valued health measurements into binary deficits (healthy or unhealthy). This classification is not standardized and is often done by using thresholds for medical intervention or maximally predictive values from statistical tests. This work proposes a simple and generic methodology for the creation of FI from laboratory values and measures its performance against existing methods. The methodology is as follows: a direction of risk is determined for each measurement, individuals are then assigned a score based on their relative standing in the population, binarization is then done using a global cut-point which binarizes all measures based on a given quantile. This method is shown to outperform FI created with medical risk thresholds for a range of global cut-points in