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Older Chinese Americans face many socioeconomic barriers including limited English proficiency, low educational levels, and limited access to care. These socioeconomic disadvantages not only contribute to an increased risk of developing dementia but also worsen inequitable access to effective strategies to promote cognitive health. Cognitive training is shown to be beneficial to maintain or enhance cognitive function. However, most prior interventions were tested exclusively on non-Hispanic Whites. To address this gap, we aim to adapt empirically supported cognitive training activities into a culturally and linguistically relevant mHealth cognitive training intervention. The adaptation process of the cognitive training includes focus groups (n=6/group) with older Chinese Americans (3 groups) and adult children (2 groups) to adapt cognitive training components to our target population. We will then organize an experience-based co-design workshop to further refine the intervention. Engaging end-users early will optimize the development of a culturally and linguistically relevant cognitive training intervention.

**SOCIAL ISOLATION, SLEEP DISTURBANCE, AND COGNITIVE HEALTH: A LONGITUDINAL MEDIATION STUDY**

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Research indicates that social isolation is associated with dementia, but the role of sleep on this association is less known. We aimed to examine the impact of social isolation on cognitive function, and how sleep disturbance mediated the association. Data came from the 2006, 2010, and 2014 waves of the Health and Retirement Study. Participants aged 50+ who completed the Psychosocial and Lifestyle Questionnaire in 2006 were included (n=5,036). Measures include the Social Isolation Index, modified Jenkins Sleep Scale, and Telephone Interview of Cognitive Status. Cross-lagged panel models were used in the analysis. After controlling socio-demographics, lifestyle, and loneliness, social isolation predicted subsequent sleep disturbance (β=-0.05; P<0.01), which in turn predicted worse cognitive functioning (β=-0.02; P<0.01). The reverse pathways from cognitive function to social isolation were also statistically supported. Public health initiatives could reduce sleep disturbance by facilitating social integration and participation in community activities, thereby protecting against cognitive decline.

**LONELINESS AND ACCELERATED COGNITIVE DECLINE: MEDIATION EFFECTS OF RESILIENCE AND PURPOSE OF LIFE**

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Drawing from the Conservation of Resources Theory, we aim to understand the implications of loneliness on psychological resources (i.e., resilience and purpose in life) and cognitive health in later life. This study utilizes data (2006-2018) from the Health and Retirement Study to examine pathways, both direct and indirect through psychological resilience and purpose in life, from loneliness to cognitive trajectories over time. Respondents reporting higher levels of loneliness had worse initial cognitive function (β=-0.43; P<0.01) and accelerated cognitive decline (β=-0.05; P<0.01). Feeling lonely is associated with reduced resilience (β=-0.23; P<0.01) and purpose in life (β=-0.17; P<0.01) which, in turn, are associated with worse cognitive health. Finally, pathway analyses confirm that loneliness is indirectly associated with initial cognitive health and accelerated cognitive decline through deteriorating psychological resources. Positive psychological interventions can be beneficial by promoting resilience and purpose in life and subsequently improve cognitive health.

**THE TRAJECTORY OF FAMILY FUNCTION OF STROKE SURVIVORS AND ITS IMPACT ON COGNITIVE IMPAIRMENT: A LONGITUDINAL STUDY**

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This study examined the trajectory of family function of Chinese stroke survivors and its impact on cognitive impairment. We conducted a prospective longitudinal study and assessed family function of 170 stroke survivors and their family caregivers by Family Assessment Device (FAD) during acute stage and at 3, 6 months after onset via face-to-face follow-ups interview in Nanjing, China from January to October, 2020. Group-based Trajectory Model was applied to analyze trajectories of family function. Family function deteriorated with time. Four patterns of FAD trajectory (A: dysfunction-deterioration-improvement; B: severe dysfunction-stable; C: healthy function-rapid deterioration; D: approximate healthy function-stable) were identified. Healthy and stable family function was associated with better cognition and quality of life (β=-0.216, p<0.05, β=-0.159, p<0.05, respectively). Future studies are needed to further explore the reason why family function deteriorated and the linkage between family function and stroke survivors’ outcomes.

**SESSION 1140 (BIOLOGICAL SCIENCES INVITED SYMPOSIUM)**

**SYSTEMS BIOLOGY OF AGING**

Chair: Timothy Rhoads

Program Overview: Aging is a complex process; numerous aspects of cell and animal physiology change with age and pinpointing a single causal mechanism has proven difficult. A systems-level approach, which attempts to integrate multiple perspectives of aging into a more cohesive understanding, addresses this challenge by leveraging the explosion of genomic, proteomic, and molecular data.
in recent years of molecular and biological “big data.” In this session, speakers will describe their efforts using systems biology approaches to achieve a multivariate assessment of the mechanisms of aging. Dr. Gladyshev will speak on recent work to understand the systemic mechanisms that underpin lifespan control. Dr. Levine moves the focus to epigenetic measures of aging, an emerging biomarker. Dr. Kane will describe efforts to examine frailty phenotypes and their biological underpinnings, as well as sexual dimorphism during aging in mice. Dr. Rhoads will describe the broad landscape of RNA processing, a mechanism with a recently described association with aging and delayed aging by caloric restriction, in multiple organisms and tissue contexts, as well as engagement of this mechanism during different aging interventions. Together our speakers advance our understanding of the multifactorial nature of aging biology and set the stage for the development of interventions that target all aspects of the aging process.

**RNA PROCESSING MECHANISMS DURING AGING AND CALORIC RESTRICTION**

Timothy Rhoads, Josef Clark, and Rozalyn Anderson, University of Wisconsin-Madison, Madison, Wisconsin, United States

Caloric restriction (CR), a reduction in caloric intake without malnutrition, was first described in the 1930s and is a robust model to extend lifespan. While the specific mechanisms that produce delayed aging are still unknown, work has demonstrated the importance of metabolism – dysregulated mitochondrial metabolism is an aging hallmark, while CR upregulates energy metabolism. Crucially, transcriptional regulation plays a key role in implementing this metabolic program although details are still unclear. Splicing factors that are required for the beneficial effects of dietary restriction in nematodes have been identified, and large-scale exon usage changes have been observed across the metabolic network engaged by CR in various tissues from non-human primates, suggesting a translational mechanism that might contribute to how CR delays aging. We will discuss the landscape of RNA processing across multiple organism, tissue, and intervention contexts and provide a broad perspective of how RNA processing contributes to enhanced longevity.

**INVESTIGATION OF BIOLOGICAL DETERMINANTS OF FRAILTY IN MALE AND FEMALE MICE**

Alice Kane1, Patrick Griffin2, Matthew Arnold3, Maeve McNamara2, Daniel Vera4, David Vogel4, and David Sinclair5, 1. Institute for Systems Biology, Seattle, Washington, United States, 2. Harvard Medical School - Blavatnik Institute, Boston, Massachusetts, United States, 3. Harvard Medical School, Boston, Massachusetts, United States, 4. Volo Foundation, Jupiter, Florida, United States

Frailty is quantified as the accumulation of health deficits over an organism’s lifetime and gives a measure of the overall health of an organism. Preliminary studies have found an association between frailty and some of the hallmarks of aging including inflammation and senescence. However, the molecular underpinnings of frailty, and whether the mechanisms of frailty are distinct from or overlap those of aging is unknown. Previously we developed clocks based on frailty assessments that accurately predict age and lifespan in older male mice. Here, we expand these clocks to predict age, lifespan and frailty itself in younger, and also female mice. Additionally, we incorporate molecular measures including blood cell composition, plasma metabolomics, PBMC DNA methylation and stool microbial diversity measures into the clocks. These clocks provide important tools for the field, and also provide an indication of the molecular underpinnings of frailty and sex differences in these.

**SYSTEMS AGING AND REJUVENATION**

Vadim Gladyshev, Brigham and Women’s Hospital, Boston, Massachusetts, United States

What is aging? When does it begin? How to control lifespan? Can we rejuvenate organisms in addition to slowing down the aging process? There is no consensus on these questions, but recent developments in the field may allow to address these questions. In particular, DNA methylation of defined sets of CpG dinucleotides emerged as a critical and precise biomarker of the aging process. Multi-variate machine learning models, known as epigenetic clocks, exploit quantitative changes in the methylome to predict the age of bulk tissue with remarkable accuracy. Additionally, the first epigenetic aging clock that works at the level of single cells has been developed. Together with advances in genomics, transcriptomic longevity signatures and intervention strategies, these tools support quantification and manipulation of the aging process. Moreover, these tools may also be used to assess the possibility of age reversal. Several types of rejuvenation have been described, including the recently discovered process of early embryonic rejuvenation, culminating in ground zero, marking the beginning of organismal aging.

**SYSTEM SPECIFIC AGING SCORES: A STATE OF THE ART AGING CLOCK BUILT USING AGING SCORES FROM DIFFERENT BODILY FUNCTIONS**

Raghav Sehgal1, Albert Higgins-Chen1, Margarita Meer2, and Morgan Levine2, 1. Yale University, New Haven, Connecticut, United States, 2. Altos Labs San Diego Institute of Science, San Diego, California, United States

Aging is a highly heterogeneous process at multiple levels. Different individuals, organs, tissues, and cell types are inately diverse and age in quantitatively different manners. Epigenetic clocks have been developed to capture overall degree of aging and typically report a single biological age value. However, single measures fail to provide insight into differential aging across organ systems. Our aim was to develop novel systems-specific methylation clocks, that when assessed in blood, capture distinct aging subtypes. We utilized three large human cohort studies and employed both supervised and unsupervised machine learning models by linking DNA methylation to lower dimensional vectors composed of system specific clinical chemistry and functional assays. In doing so, we were able to develop 11 unique system-specific scores—heart, lung, kidney, liver, brain, immune, inflammatory, hematopoietic, musculoskeletal, hormonal, and metabolic. We observe that in independent data, the specific systems relate to meaningful outcomes—for instance the brain score is strongly associated with cognitive functioning;