energy level over time (N=94, defined as decline <1.0 SD below the mean) had significantly higher FC in the striatal-associative network (mean difference [95% CI]: 0.041 [0.00192,0.0807], p=0.04). Associations were similar when adjusted for brain atrophy, demographics, and education. Although based on subjective measures, the distinct spatial patterns of these associations support our hypothesis that neural basis of energy and fatigue may differ.

Session 3435 (Symposium)

MULTISCALE BRAIN AGING IN THE CONTEXT OF NEURODEGENERATION AND ALZHEIMER’S DISEASE
Chair: Kyra Thrush Co-Chair: Yaroslav Markov
The brain, with a diverse array of specialized cells, regional substructures, and a relatively isolated microenvironment, represents a uniquely challenging organ system for aging research. The brain can experience physical trauma, interact with the periphery, and is responsible for cognitive and behavioral modifications that can feed back into the molecular processes of aging both within and external to the brain. Advances to our understanding and ability to intervene in the complexity that personifies brain aging and associated neurodegeneration will require integrated, multiscale approaches operating in tandem. Therefore, we have organized this symposium to highlight promising new approaches to study brain aging through the lens of multiple biological levels of organization. We will provide insight not only into normal brain aging, but will also suggest key spurious processes that may drive neurodegeneration and functional decline.

DEEP LEARNING METHODS CAPTURE NON-LINEAR BRAIN AGING PATTERNS UNDERLYING ALZHEIMER’S DISEASE AND RESILIENCE
Albert Higgins-Chen, Yaroslav Markov, Raghav Sehgal, Morgan Levine, and Kyra Thrush, Yale University, New Haven, Connecticut, United States
The current era of multi-omics data collection has enabled researchers to obtain exceptionally comprehensive profiling of disease subjects. However, exceptionally high dimensionality can ultimately be an obstacle to biological insight. Previously, we presented a method in which penalized regression of methylation principal components reduces noise and improves prediction of age, disease, and Alzheimer’s Disease (AD) pathophysiology. However, strictly linear methods may overly simplify the complex epigenetic aging landscape. We hypothesized that non-linear deep learning methods could identify molecular signatures that better reflect individual resilience to AD. Through the use of an autoencoder to represent high dimensional methylation array data, and supplemental machine learning methods, we connect latent nonlinear representations of the brain to aging, resilience, and indications of AD. In particular, resultant age-predicting representations of methylation were correlated with enrichment of methylation regions and biological pathways. Contextualized within AD pathology, this work provides valuable, ongoing insight into resilience in AD.

THE ARC OF ASTROCYTE AGING: INSIGHTS FROM SCRNASEQ
Christopher Minteer,1 Morgan Levine,2 and Margarita Meer,3 1. Yale University, Yale University, Connecticut, United States, 2. Yale University, New Haven, Connecticut, United States, 3. Yale School of Medicine, New Haven, Connecticut, United States
There is an urgent need to increase our understanding of brain aging and its role in neurodegeneration. While, evidence suggest that many hallmarks of aging, including epigenetic alterations and cellular senescence may be implicated in dementia, studying these and other progressive molecular changes in the brain remains extremely challenging. We asked whether something as simple as artificially aging cells in culture could recapitulate the changes that occur during organismal aging. To test this, we passaged human primary astrocytes and performed single-cell RNA sequencing (scRNAseq) of cells at passages 2-10. We observe that the sequential passaging—that terminates with a cluster of senescent cells—can be captured by manifolds and used to quantify a pseudo-time measure of progressive transcriptional changes. We identify genes underlying this transition and apply this signature of in vitro astrocyte passaging to scRNAseq from human and mouse brain aging studies, demonstrating associations with aging and neuropathology.

NEURONAL EXCITATORY STATE IS LINKED TO STRESS RESILIENCE
Bruce Yankner, and Joseph Zullo, Harvard Medical School, Boston, Massachusetts, United States
The aging human brain is a study in both the importance and limitations of human stress response factors. Individual neurons can maintain functionality for 80 or more years, testifying to the potency of their stress response pathways. However, failure of these pathways during aging drastically increases the risk of neurodegenerative diseases. The transcriptional repressor REST is induced in the brains of long-lived humans but is lost in neurodegenerative disease. Here, we explore one modality of REST’s protective effects: regulation of neuronal excitability. We show that excitatory capacity and stress response are inversely correlated in the human brain. We find that REST and its C. elegans orthologs repress neuronal excitation in response to stressful conditions. Further, exogenously suppressing neuronal excitation restores stress resistance to REST-deficient animals, while enhancing stress response in wildtype ones. Thus, regulation of neuronal activity is an important aspect of neuronal stress response and a potential therapeutic modality.

EARLY PREDICTION OF COGNITIVE DEFICITS AFTER TRAUMATIC BRAIN INJURY BASED ON AD-LIKE PATTERNS OF NEURODEGENERATION
Alexander Maher,1 Kenneth Rostowsky,2 Nikhil Chaudhari,1 Nahian Chowdhury,1 Elliot Jacobs,1 David Robles,1 Ammar Dharani,2 and Andrei Irimia,2 1. University of Southern California, Los Angeles, California, United States, 2. University of Southern California, University of Southern California, California, United States
Traumatic brain injuries (TBIs) are frequently followed by persistent brain alterations and by cognitive sequelae, especially in older adults. Although mild TBI (mTBI) is a risk factor for Alzheimer’s disease (AD), the extent to which the two conditions are related remains largely unexplored. Using structural, functional and diffusion magnetic resonance imaging (MRI), we have identified AD-like post-traumatic neurodegeneration patterns that accurately prognosticate...
cognitive decline after geriatric mTBI. Our results indicate that these features involve cortical regions and circuitry mediating memory and executive function, and that AD neurodegeneration has key structural and functional similarities to post-traumatic neurodegradation. Using machine learning of such similarities, we have accurately forecast the severity of chronic cognitive deficits after geriatric mTBI based on acute neuroimaging measures. Our findings demonstrate that AD-like alterations in brain structure and function observed early after injury can predict post-traumatic mild cognitive impairment, which is itself strongly associated with AD risk.

EXERCISE-ASSOCIATED PATHWAYS AS NOVEL NEUROPROTECTANTS AGAINST CNS AGING AND ALZHEIMER’S DISEASE

Constanza Cortes, University of Alabama at Birmingham, University of Alabama at Birmingham, Alabama, United States

Skeletal muscle has recently arisen as a novel regulators of Central Nervous System (CNS) function and aging, secreting bioactive molecules known as myokines with proteostasis and metabolism-modifying functions in targeted tissues. We have recently generated a novel transgenic mouse with enhanced muscle proteostasis via moderate overexpression of Transcription Factor E-B (TFEB), a powerful master regulator of cellular clearance and proteostasis. We have discovered that the resulting enhanced skeletal muscle proteostasis function can significantly ameliorate proteotoxicity in the aging CNS and improve cognition and memory in aging mice. These neuroprotective benefits are markedly reminiscent of those observed in the aging CNS post-exercise, suggesting enhancing muscle proteostasis may be sufficient to replicate the local and systemic effects of exercise. Identification of pathways regulating crosstalk between skeletal muscle and CNS may yield targets with high therapeutic potential for diseases of the aging CNS.

Session 3440 (Paper)

NURSING HOME STAFF

COVID-19 IMPACT ON ALBERTA NURSING HOME WORKERS: AN INTERPRETIVE DESCRIPTIVE STUDY WITH DIRECT CARE PROVIDERS

Jude Spiers,1 Heather Tilty,1 Amber Savage,1 Trina Thorne,1 Sandra Young,2 Neda Asadi,3 Corinne Schalm,4 and Carole Estabrooks1 1. University of Alberta, Edmonton, Alberta, Canada, 2. University of Alberta, University of Alberta, Alberta, Canada, 3. University of Alberta, University of Alberta, Alberta, Canada, 4. Alberta Health, Alberta Health, EDMONTON, Alberta, Canada

COVID-19 has devastated the LTC sector, but we lack systematic information on the impact on frontline staff. Our research, a partnership with the continuing care branches of Alberta Health and Alberta Health Services, was aimed at assessing COVID-19 impacts on staff’s well-being and quality of work-life and quality of care and life among residents. Here we report on staff. Using an interpretive descriptive approach, we interviewed 140 staff from January through April 2021, in 34 nursing homes. Facilities selected varied in ownership (public/private) and COVID-19 status (high, moderate, or low incidence). Virtual interviews focused on three key areas of impact: (a) staff mental and physical health, well-being, and work-life, (b) the facility, and (c) on residents. Interviews were analyzed using inductive content analysis. Dominant themes included a commitment of staff to resident wellbeing; a norm of stoicism in which accumulative stress of COVID-19 is recognized in participants’ private lives but not their work; the critical role of teamwork in managing extra workload associated with COVID-19 protocols; role flexibility, particularly managers’, enables workers to minimize interruptions to care activities; governmental wage subsidies and the restriction of workers to only one facility benefits residents and workers in terms of time and familiarity, but some health care aides faced a wage reduction of 30-40%, Alongside the research component, we regularly met with stakeholders and end-users to discuss emerging findings and potential areas needing urgent intervention, as well as longer-term programming as the impact of COVID-19 will persist for many years.

FACTORs INFLUENCING RESIDENT RESPONSIVE BEHAVIORS TOWARD STAFF IN NURSING HOMES: A SYSTEMATIC REVIEW

Lori Weeks,1 Abubakar Mohamed Nassur,2 Fajr Haq,3 Viraji Rupasinghe,4 Carole Estabrooks,3 and Yuting Song,5 1. Dalhousie University, Dalhousie University, Nova Scotia, Canada, 2. University of Alberta, University of Alberta, Alberta, Canada, 3. University of Calgary, Calgary, Alberta, Canada, 4. Dalhousie University, Halifax, Nova Scotia, Canada, 5. University of Alberta, Edmonton, Alberta, Canada

When staff experience various types of resident responsive behaviors, this can lead to decreased quality of work-life and lower quality of care. We synthesized empirical quantitative and qualitative evidence on factors associated with resident responsive behaviors directed towards staff in nursing homes. We searched 12 bibliographic databases and “grey” literature with two key words: long-term care and responsive behaviors resulting in 7671 sources. Pairs of reviewers independently completed screening, data extraction, and risk of bias assessment. Based on extracted data, we developed a coding scheme of factors utilizing the ecological model as an organizational structure. We then applied the coding scheme to quantitative and qualitative articles and prepared narrative summaries for each factor. From 86 included studies (57 quantitative, 28 qualitative, 1 mixed methods), multiple factors emerged, such as staff training about responsive behaviors (individual level); staff approaches to care (interpersonal level); leadership, staffing resources, and physical environment (institutional level); and racism and patriarchy (societal level). Quantitative and qualitative results each provided key insights, such as qualitative results pertaining to leadership responses to reports of responsive behaviors, and quantitative findings on the impact of staff approaches to care on responsive behaviors. By synthesizing both quantitative and qualitative evidence, this review provides a comprehensive