tired during follow-up (N=119) had significantly lower FC in the striatal-limbic network (mean difference [95%CI]: -0.055 [-0.1020,-0.00879], p=0.02). Participants with stable 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

Kyra Thrush, Albert Higgins-Chen, Yaroslav Markov, Raghav Sehgal, and Morgan Levine, *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

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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

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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

Andrei Irimia,[1] Alexander Maher,[2] Kenneth Rostowsky,[1] Nikhil Chaudhari,[2] Nahian Chowdhury,[2] Elliot Jacobs,[2] David Robles,[2] and Ammar Dharani,[2] *1. University of Southern California, University of Southern California, California, United States, 2. University of Southern California, Los Angeles, California, United States*

Traumatic brain injuries (TBIs) are frequently followed by persistent brain alterations and by cognitive sequalae, especially in older adults. Although mild TBI (mTBI) is a risk