older adults free of neuropathologies and clinically overt conditions. This symposium will first present clinical and epidemiologic justifications for operationalizing energy as a separate construct from fatigue and then will provide evidence on the underlying neurobiological correlates. Taken together, our results suggest perceived energy: a) overlaps with but is distinct from lower fatigability (Katz); b) may signal resilience against age-related declining mood and gait speed despite self-reported tiredness (Ehrenkranz); c) appear negatively influenced by Alzheimer's neuropathology (Dougherty); and d) may reflect a distinct spatial distribution of brain functional connectivity (Hengenius). Thus, this symposium will explore energy as a mechanism related to yet distinct from fatigue and its implications for both healthy aging and neuropathological processes.

ENERGY AND FATIGUE PREDICT GAIT SPEED AND MOOD DECLINE: RESULTS FROM THE HEALTH, AGING AND BODY COMPOSITION STUDY

Rebecca Ehrenkranz,[1] Xiaonan Zhu,[2] Nancy W. Glynn,[3] and Caterina Rosano,[2] *1. University of Pittsburgh Graduate School of Public Health, Pittsburgh, Pennsylvania, United States, 2. University of Pittsburgh, Pittsburgh, Pennsylvania, United States, 3. University of Pittsburgh Graduate School of Public Health, Pittsburgh, Pennsylvania, United States*

Older adults may report high energy alongside tiredness or vice versa; little is known about whether discordant self-reported energy (SEL) and tiredness predict trajectories of mood, cognition, or gait speed. SEL (0-10 scale dichotomized at median) and tiredness (present/absent) were obtained in 2,613 older adults (aged 74.6± 2.87 years) and used to create four groups (energized/not tired, low energy/tired, energized/tired, low energy/not tired). Center for Epidemiologic Studies Depression Scale (CES-D) and gait speed were measured over 10 years; mixed effect models compared trajectories in these domains across each group with low energy/tired group as referent. Each group was significantly associated with CES-D and gait. Adjusting for demographics, the high SEL/not tired group showed the least decline in mood (ß = -0.17, p<0.01); the high SEL/tired group showed the least decline in rapid gait (ß = 0.008, p = 0.02). High SEL may indicate resilience for mood and gait speed decline.

ENERGY AND EXHAUSTION MAY EXPLAIN DIFFERENT SUBDOMAINS OF PERCEIVED FATIGABILITY

Rain Katz,[1] Rebecca Cohen,[1] Theresa Gmelin,[1] Kyle Moored,[2] Yujia (Susanna) Qiao,[3] Maggie Slavin,[1] and Nancy W. Glynn,[4] *1. University of Pittsburgh Graduate School of Public Health, Pittsburgh, Pennsylvania, United States, 2. University of Pittsburgh, Pittsburgh, Pennsylvania, United States, 3. University of Pittsburgh, University of Pittsburgh, Pennsylvania, United States, 4. University of Pittsburgh Graduate School of Public Health, Pittsburgh, Pennsylvania, United States*

Fatigability is a more sensitive measure of one's perception of fatigue. To identify an appropriate fatigue question when a fatigability measure is unavailable, we examined associations between widely used global fatigue questions and perceived physical and mental fatigability. Participants (N=896, age=74.7±6.6, 58.1% women) from two aging research registries completed the valid Pittsburgh Fatigability Scale (PFS, 0-50) and five global fatigue questions: energy level (0-10), running out of energy (0-5), feeling energetic (0-6), feeling tired (0-6), and feeling exhausted (0-6) over past four weeks. All fatigue measures were correlated (p<0.0001) with physical (|r| range=0.48-0.57) and mental fatigability (|r| range=0.31-0.39). "Energy level" and "feeling exhausted" had strongest associations with physical and mental fatigability, respectively, in age, sex, BMI-adjusted regression models (p's<0.001), suggesting older adults can distinguish between physical and mental domains. Future work will explore how these constructs are distinct but related, and confirm the optimal proxy for the two fatigability subdomains.

ASSOCIATION OF WALKING ENERGETICS WITH AMYLOID STATUS: FINDINGS FROM THE BALTIMORE LONGITUDINAL STUDY OF AGING

Ryan Dougherty,[1] Fangyu Li,[1] Amal Wanigatunga,[1] Qu Tian,[2] Eleanor Simonsick,[3] Murat Bilgel,[2] and Jennifer Schrack,[1] *1. Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, United States, 2. National Institute on Aging, Baltimore, Maryland, United States, 3. National Instute on Aging/NIH, Baltimore, Maryland, United States*

Higher energetic costs for mobility are associated with slow and declining gait speed. Slow gait is linked to cognitive decline and Alzheimer's disease (AD), but the physiological underpinnings are note well-understood. We investigated the cross-sectional association between the energetic cost of walking and amyloid status (+/-) in 174 cognitively unimpaired men and women (52%) aged 78.5±8.6 years. The energetic cost of walking was assessed as the average oxygen consumption (VO2) during 2.5 minutes of customary-paced overground walking. Amyloid status was determined from 11C-Pittsburgh compound B (PiB) positron emission tomography (PET) imaging. Average energetic cost of walking was .169±.0379 ml/kg/m and 30% of the sample was PiB+. In logistic regression adjusted for demographics, APOE-e4, body composition and comorbidities, each 0.01ml/kg/m higher energy cost was associated with 12% increased odds of being PiB+ (OR=1.12; 95% CI:1.01-1.24). Inefficient walking may be a clinically meaningful physiological indicator of emerging AD-related pathology.

CORTICO-STRIATAL FUNCTIONAL CONNECTIVITY REFLECTS CHANGES IN SUBJECTIVE ENERGY AND TIREDNESS

James Hengenius,[1] Rebecca Ehrenkranz,[2] Theodore Huppert,[1] and Caterina Rosano,[1] *1. University of Pittsburgh, Pittsburgh, Pennsylvania, United States, 2. University of Pittsburgh Graduate School of Public Health, Pittsburgh, Pennsylvania, United States*

Subjective feelings of energy and tiredness may reflect different neural processes. Functional connectivity (FC) was measured in 272 HealthABC participants via resting state functional MRI in striatal-associative, striatal-limbic and striatal-sensorimotor networks. Subjective energy level (scored 1-10) and tiredness (tired/not-tired) during the prior month were collected via self-report from year 2 to year 10 (mean energy follow-up=8 years, tiredness follow-up=7 years). Participants who never reported being

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

Margarita Meer,[1] Christopher Minteer,[2] and Morgan Levine,[3] *1. Yale School of Medicine, Yale University, Connecticut, United States, 2. Yale University, Yale University, Connecticut, United States, 3. Yale University, 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

Joseph Zullo, and Bruce Yankner, *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

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