examining the number of events as a continuous variable (p=0.003) or when looking at dose-response.
Conclusions: Overall, our results suggest that one process in which experiences of trauma may impact health is via its effect on the biological aging process.
Keywords: Aging, DNA Methylation, Psychosocial Stress, Trauma Exposure

231. Posttraumatic Psychopathology and a Quickening Pace of the Epigenetic Clock

Erika Wolf[1], Mark Logue[2], Filomene Morrison[3], Anjanette Stone[4], Steven Schichman[4], Regina McGlinchey[5], William Milberg[5], and Mark Miller[6]

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Background: Advances in the study of biological aging have identified that DNA methylation data can be used to index cellular age and to evaluate pathogenic factors that accelerate aging. Stress, trauma, and posttraumatic stress disorder (PTSD) have been cross-sectionally associated with advanced DNA methylation age relative to chronological age, however longitudinal investigation is lacking. The aim of this study was to examine longitudinal associations between an array of posttraumatic psychiatric conditions and the pace of the epigenetic clock.
Methods: 179 veterans (88% male, mean age = 33 years) completed two assessments spanning approximately two years. Whole blood DNA methylation was interrogated via the Illumina EPIC beadchip and two indices of DNA methylation age quantified. Psychiatric diagnoses were assessed via structured interview. The pace of the epigenetic clock was operationalized as the difference between age estimates over time as a function of time between assessments.
Results: In regressions, PTSD symptoms defined by avoidance of trauma-related cues and emotional numbing (p = .02) and alcohol-use disorders (p = .001) at time 1 were associated with an increasing pace of the epigenetic clock. Alcohol-use disorders were associated with 1.58 years in epigenetic age acceleration for every year between assessments.
Conclusions: This is the first study to suggest that posttraumatic psychopathology is associated with a quickening pace of the epigenetic clock over time. This carries implications for understanding premature onset of age-related diseases among individuals with chronic psychopathology. It suggests that accelerated cellular aging may be a shared consequence across stress-related psychiatric symptoms.
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Keywords: Chronic Stress, Cellular Aging, Epigenetics, Longitudinal Cohort, Alcohol Use Disorder

232. Mechanisms of Accelerated Cognitive Aging in PTSD

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Background: Older PTSD patients exhibit faster cognitive decline and have twice the risk of dementia compared to individuals without PTSD. Accelerated biological aging may explain these findings, as PTSD is associated with similar brain changes to those occurring with cognitive aging, including bilateral hippocampal volume reductions and increased microvascular lesions. This presentation describes ongoing work from our laboratories evaluating dentate gyrus (DG) metabolism and DG-dependent cognition as mechanisms of accelerated cognitive decline in PTSD.
Methods: In preliminary studies, adults with PTSD (N=15) were assessed with the Clinician Administered PTSD Scale (CAPS) and cerebral blood flow (CBV)-fMRI. In addition, individuals with PTSD (N=16) and age-matched healthy controls (N=9) were evaluated using a modified form of the Benton Visual Retention Task (ModBent), which we have previously demonstrated to be DG-dependent. Data collection for a larger version of these studies is ongoing.
Results: In a linear regression of CAPS score on CBV values in 6 regions of interest (right and left posterior DG, mid DG, and anterior DG), a significant ($p<0.05$) negative correlation was found between right anterior DG CBV and CAPS score. ModBent performance declined with increasing age with moderate effect size magnitude (r=0.30) in PTSD patients but not controls (r=-0.18).
Conclusions: PTSD is associated with relative hypometabolism in the right anterior DG and potentiated age-related decline in DG-dependent cognitive function. These findings are consistent with the hypothesis that PTSD and brain aging constitute a “double hit” to DG/CA3 that contributes to the negative health and functional outcomes suffered by older PTSD patients.
Supported By: NIMH R01 MH111596
Keywords: PTSD - Posttraumatic Stress Disorder, Brain Aging, Hippocampus, Cerebral Blood Flow

233. Indices of Cellular Health are Associated With Antidepressant Treatment Response

Daniel Lindqvist[1], Christina Hough[2], Victor Reus[2], Alexandra Morford[2], Jue Lin[2], Jill James[3], Francesco Saverio Bersani[4], Elissa Epel[2], Synthia H. Mellon[2], and Owen Wolkowitz[2]

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Background: Accelerated cellular aging, evidenced by shortened leukocyte telomere length (LTL), has been reported in Major Depressive Disorder (MDD), and may convey an increased risk for somatic co-morbidity. Shortened LTL reflects a cell's mitotic history, cellular "age" and cumulative exposure to inflammation and oxidation, as well as the availability of telomerase, a telomere-lengthening enzyme. Telomere shortening leads to replicative senescence and cellular malfunctions including oxidative stress, mitochondrial damage, and apoptosis. Here we present data linking indices of accelerated cellular aging to worse antidepressant treatment response in MDD.
Methods: Unmedicated MDD subjects were assessed before and after 8-weeks of open-label SSRI treatment.
Results: Lower antidepressant treatment efficacy was associated with i) shorter pre-treatment LTL ($p<0.05$, $n=27$), ii) smaller increases in telomerase activity over the course of treatment ($p<0.01$, $n=16$), iii) higher levels of oxidative stress markers pre-treatment ($p<0.01$, $n=22$), and iv) a greater increase in oxidative stress during treatment ($p<0.05$, $n=22$). Circulating cell free mitochondrial DNA (CCf-mtDNA), a potential marker for mitochondrial stress and cellular damage, was highly elevated was highly significantly elevated in unmedicated MDD compared to healthy controls ($p<0.00001$, $n=105$), and ccf-mtDNA increased during treatment in non-responders, but not in responders ($p=0.02$, $n=19$).
Conclusions: Our data show, from multiple indices of cellular health, that accelerated cellular aging or damage is associated with poorer antidepressant response in MDD. Cellular health may be an important moderator of successful antidepressant response.
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Keywords: Antidepressant Response, Oxidative Stress, Cellular Aging, mtDNA Copy Number, MDD

SYMPOSIUM
Transdiagnostic Neuromarkers of Emotion: From Bench to Bedside, Across Species & Development

3:00 p.m. - 5:00 p.m.
Chair: Alexander Shackman
Co-Chair: Amit Etkin

234. Neurogenetic Bases of Extreme Early-Life Anxiety

Alexander Shackman[1]

[1]University of Maryland College Park

Background: Children with an anxious temperament (AT) are at risk for anxiety disorders, depression, and substance abuse, underscoring the need to develop a deeper understanding of the underlying neurobiology.
Methods: Here, I will describe published and unpublished work leveraging multimodal brain imaging techniques (FDG-PET/fMRI/sMRI) in humans and monkeys. Monkeys are ideal for developing an understanding of the origins of extreme early-life anxiety; homologous genes and brains endow monkeys and children with a similar repertoire of defensive responses to novelty and potential threat, enabling similar procedures for quantifying trait-like differences in AT.
Results: Work using these methods ($p's<.05$) has revealed compelling evidence that AT—a heritable, multidimensional phenotype—reflects a distributed circuit encompassing the central nucleus of the amygdala (Ce), bed nucleus of the stria terminalis (BST), orbitofrontal cortex (OFC), and periaqueductal gray (PAG) ($n=592$). These regions show robust intrinsic functional connectivity in humans ($n=27$-130) and monkeys ($n=89$-378). Genetic correlation analyses indicate that this circuit can be fractionated into regions mediating heritable risk for the development of extreme anxiety (BST, OFC, PAG) vs. regions mediating risk associated with adverse experience (Ce). Reduced connectivity between Ce and prefrontal cortex is associated with heightened anxiety in monkeys ($n=89$) and pediatric anxiety patients ($n=28$). Elevated BST metabolism supports persistent anxiety following threat encounters ($n=23$-109) in monkeys and increased BST volume prospectively predicts elevated negative affect in daily life in humans ($n=44$; smart-phone experience-sampling).
Conclusions: These findings provide a framework for developing improved biomarkers of transdiagnostic risk and inform mechanistic work aimed at developing more effective interventions for pathological anxiety.
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Keywords: Fear, Anxiety, Individual Differences, Brain Imaging, Extended Amygdala (CeA/BST)

235. Novel Mechanisms of Fear Reduction Targeting the Biological State of the Developing Brain

Dylan Gee[1], Paola Odriozola[1], Luise Pruessner[2], Jason Haberman[1], and Emily Cohodes[1]

[1]Yale University, [2]Heidelberg University

Background: Anxiety disorders, which often emerge during adolescence, are characterized by difficulty discriminating between threatening and safe contexts. Translational studies