Conclusions: Distinct combinations of clinical and neural markers predict affective lability factors in the future in two independent samples of at-risk youth suggesting the utility of these variables as objective markers of future risk and potential targets for intervention
Supported By: R01MH060952 2R01 MH73953-06A1 2R01 MH73816-06A1 2R01 MH73967-06A1 2R01 MH73801-06A1
Keywords: Outcome Prediction, Bipolar Disorder, At-Risk Youth, Cortical Thickness, BOLD fMRI

SYMPOSIUM
Mitochondrial Stress and Psychiatric Disorders
3:00 p.m. - 5:00 p.m.
Chair: Josine Verhoeven
Co-Chair: Daniel Lindqvist

61. Developing Sensitive Measurements of Mitochondrial Responses to Acute and Chronic Stress

Martin Picard[1], Caroline Trumpff[1], Anna Marsland[2], Aric Prather[3], Brett Kauffman[2], Eli Puterman[4], Kirstin Aschbacher[3], Gabriel Sturm[1], James Martin[2], Judith Caroll[5], Bruce McEwen[6], Yan Burelle[7], and Elissa Epel[3]

[1]Columbia University Medical Center, [2]University of Pittsburgh, [3]University of California, San Francisco, [4]University of British Columbia, [5]University of California, Los Angeles, [6]The Rockefeller University, [7]University of Ottawa

Background: Mitochondria are complex organelles with the own genome that generate the energy required for life and produce signals that enable stress adaptation. A systematic review of animal studies suggest that acute and chronic psychological stress can damage and impair specific aspects of mitochondrial function and health. However, evaluating this possibility in humans has been difficult due to the lack of scalable measures that accurately reflect mitochondrial health.
Methods: In one study of caregivers experiencing chronic life stress, we developed an index of mitochondrial health (MHI) by measuring and integrating the activity of three mitochondrial enzymes and mtDNA copy number from frozen leukocytes. In another study where participants were exposed to acute socioevaluative stress on two separate visits, we measured pre- and post-stress circulating cell-free levels of the mitochondrial and nuclear genomes, putative signals of intracellular stress.
Results: The MHI was sensitive to previous day mood and showed superior effect size ($n=85$, $d=0.63$, $p<0.01$) comparing groups, compared to individual enzymatic and molecular measures (all $d=0.11$-0.36, n.s.). In healthy men and women, acute psychological stress triggered robust increases in circulating cell-free mtDNA (ccf-mtDNA, $n=36$, $n2=0.57$, $p<0.0001$), but not circulating nuclear DNA.
Conclusions: We describe a new integrative index of mitochondrial health that can be applied to frozen blood leukocytes, and an approach to quantify the selective release of ccf-mtDNA. Building from these examples, this presentation will also review and discuss currently available methodologies to assess mitochondrial health and mitochondrial allostatic load (MAL) in human samples.
Supported By: NIA, NIGMS, Wharton fund
Keywords: Mitochondria, Chronic Stress, Mood, Laboratory Measurements, Systematic Review

62. Circulating Cell-Free Mitochondrial DNA – a Novel Marker of Mitochondrial Stress Associated With Suicidality and Major Depressive Disorder

Daniel Lindqvist[1], Owen Wolkowitz[2], Martin Picard[3], Lars Ohlsson[4], Francesco Saverio Bersani[5], Johan Fernström[6], Åsa Westrin[6], Christina Hough[2], Jue Lin[2], Cécile Grudet[6], Lennart Ljunggren[4], Lil Träskman-Bendz[6], Victor Reus[2], Elissa Epel[2], and Synthia H. Mellon[2]

[1]Lund University/UCSF, [2]University of California, San Francisco, [3]Columbia University, [4]Malmö University, [5]Sapienza University of Rome, [6]Lund University

Background: Mitochondrial DNA copy number (mtDNA-cn), which represents the number of mitochondrial genomes per cell, can be quantified in peripheral blood mononuclear cells (PBMC) and is thought to reflect variations in mitochondrial biogenesis. Additionally, mtDNA may be released at low levels into the circulation from mitochondria under cellular stress, resulting in circulating cell-free mtDNA (ccf-mtDNA) detectable in plasma. The source or physiological significance of ccf-mtDNA in psychiatric illness is unknown but may reflect cell damage, cell death, or bioenergetic compromise.
Methods: We enrolled suicide attempters (across diagnoses), non-suicidal subjects with Major Depressive Disorder (MDD), and healthy controls (all medication-free) in two independent cohorts ($n=110$ & $n=74$). MtDNA was quantified in cell-free plasma and in PBMCs.
Results: Ccf-mtDNA was elevated in suicide attempters and in non-suicidal MDD subjects, compared to healthy controls. These group effects were very large (Cohen's d ranging from 0.9 to 4.0, all $p<0.00001$). Ccf-mtDNA and cellular PBMC mtDNA-cn were not significantly correlated with each other ($r=0.02$, $p=0.87$), suggesting they reflect different processes. Ccf-mtDNA correlated with post-dexamethasone cortisol ($r=0.5$, $p<0.001$), suggesting that HPA-axis hyperactivity may be associated with cellular damage and release of ccf-mtDNA into the blood. Ccf-mtDNA also directly correlated with the antioxidant enzyme glutathione peroxidase ($r=0.32$, $p=0.001$), possibly reflecting a compensatory attempt to upregulate antioxidant defence mechanisms due to cellular stress.
Conclusions: Ccf-mtDNA may represent a novel marker of cellular stress, which is increased in certain psychiatric conditions. These results call for replication in larger cohorts and in longitudinal studies.
Supported By: This study was funded by grants from the National Institute of Mental Health (NIMH) (Grant Number R01-MH083784), the O'Shaughnessy Foundation, the Tinberg family, and grants from the UCSF Academic Senate, the UCSF Research Evaluation and Allocation Committee (REAC), and the Bernard and Barbro Foundation. This project was also

supported by National Institutes of Health/National Center for Research Resources (NIH/NCRR) and the National Center for Advancing Translational Sciences, National Institutes of Health, through UCSF-CTSI Grant Number UL1 RR024131. The contents of this publication are solely the responsibility of the authors and do not necessarily represent the official views of the NIH. Daniel Lindqvist was supported by the Swedish Research Council (registration number 2015-00387), Marie Sklodowska Curie Actions, Cofund (Project INCA 600398), the Swedish Society of Medicine, the Söderström-Königska Foundation, the Sjöbring Foundation, OM Persson Foundation and the province of Scania (Sweden) state grants (ALF). The Blackburn lab is supported in part by gifts from the Shaklee Corporation and the Mars, Incorporated.

Keywords: mtDNA Copy Number, Major Depressive Disorder (MDD), Suicide Attempts, Circulating Cell-Free DNA, Antioxidant Enzymes

63. Socioeconomic Disadvantage and Whole Blood Mitochondrial DNA Copy Number Decline Over 10-Years: The Coronary Artery Risk Development in Young Adults (CARDIA) Cohort

Robert-Paul Juster[1], Nancy Adler[2], Martin Picard[3], Elissa Epel[2], Barbara Sternfield[4], Karen Matthews[5], David Jacobs[6], and Eli Puterman[7]

[1]Columbia University & New York State Psychiatric Institute, [2]University of California, San Francisco, [3]Columbia University, [4]Kaiser Permanente Northern California, [5]University of Pittsburgh, [6]University of Minnesota, [7]University of British Columbia

Background: Low socioeconomic status (SES) predicts poor health throughout life. One's subjective social status (SSS) can be an even stronger predictor of health than SES. We assessed SES and SSS in relation to 10-year changes in whole-blood mitochondrial DNA copy number (mtDNAcn), an emerging cellular aging biomarker.

Methods: Years 15 and 25 CARDIA data for 992 black and white men and women aged 33-47 were analyzed. SSS was assessed using the MacArthur Ladder Scale representing self-ranked standing (1-9 scale) within the community. mtDNAcn was measured by quantitative PCR. We employed linear mixed modeling to estimate baseline (Y15) and 10-year mtDNAcn rate of change (Y15 to Y25) as a function of either education, income, or SSS at Y15 in three independent analyses while adjusting for the other two variables and age, sex, race/ethnicity, physical activity, and BMI.

Results: SES did not predict baseline or changes in mtDNAcn. By contrast, higher SSS was significantly associated with lower baseline (b=-7.76, 95%CI=-13.06, -2.47) and a slower rate of decline over 10-years (SSS*time interaction: b=6.27, 95%CI=0.65, 11.89). Follow-up analysis revealed that the estimated rate of decline in mtDNAcn over 10-years was -47.58 (95%CI=-60.10, -35.06) for those 1SD above the SSS mean and -67.49 (95%CI=-79.99, -54.99) below the SSS mean.

Conclusions: Greater SSS was associated with lower mtDNAcn at baseline and also delayed DNA loss over 10-years. Irrespective of objective SES, it is possible that higher subjective social standing contributes to stress-related mitochondrial cellular aging in early adulthood but is not associated with long-term declines.

Supported By: The CARDIA study is supported by contracts HHSN268201300025C, HHSN2682 01300026C, HHSN268201300027C, HHSN268201300028C, HHSN26820 1300029C and HHSN268200900041C from the National Heart, Lung, and Blood Institute (NHLBI), the Intramural Research Program of the National Institute on Aging (NIA) and an intra-agency agreement between NIA and NHLBI (AG0005). Cell aging assays were supported by the John & Catherine MacArthur Foundation Research Network on Socioeconomic Status and Health and by the National Heart, Lung and Blood Institute of the National Institutes of Health under award number K99/R00 HL 109247. Robert-Paul Juster is funded by the Canadian Institutes of Health Research Banting Postdoctoral Award.

Keywords: Mitochondria, Socioeconomic Status, Psychosocial Stress, Depressive Symptoms

64. Early Stress and Mitochondrial DNA in Human and Mouse Models

Audrey Tyrka[1], Kathryn Ridout[2], Stephanie Parade[3], Mizan Gaillard[2], Ronald Seifer[4], Hung-Teh Kao[2], Barbara Porton[2], Lawrence Price[1], and Kevin Bath[2]

[1]Butler Hospital - Brown Medical School, [2]Brown University, [3]Bradley Hospital - Brown Medical School, [4]Bradley Hospital - Brown University

Background: Recent studies have implicated mitochondria in the effect of early trauma on risk for psychiatric disorders. Here we present results of a study of preschool-aged maltreated children and a study of a mouse model of early life stress (ELS).

Methods: Study 1: Children aged 3-5 were identified through the local child welfare agency (n=133, maltreated) or preschools and pediatric clinics (n=117, control). Home visits at baseline and 6-month follow-up included assessments of stressors and symptoms, and saliva collection for DNA and qPCR measurement of mitochondrial DNA copy number (mtDNAcn).

Study 2: C57BL/6N male mice were unhandled (UHC) or reared with restricted bedding materials from p4-p11 (ELS). Hippocampal samples across development (N=5/cell) from ≥2 different litters were isolated and cDNA synthesized. Mitochondrial oxidative genes (NADH:ubiquinone oxidoreductase subunits 1-6; cytochrome b; cytochrome c oxidase I-III; ATP synthase 6 and 8) were run in multiplex with 18S as standard.

Results: Study 1: Maltreatment was associated with higher mtDNAcn ($p<.05$). Baseline mtDNAcn was positively associated with baseline internalizing behaviors ($p<.05$), and follow-up mtDNAcn was associated with baseline and follow-up internalizing ($p's<.005, <.0001$).

Study 2: Gene expression increased with development ($p's<.0001$). ELS significantly reduced expression of a number of mitochondrial genes ($p's<.05$), particularly at p28 and p50.

Conclusions: This is the first evidence of altered mtDNAcn with stress in children; results are consistent with data from