National Institutes of Health

Diversity Supplement Professional Development and Networking Workshop

Book of Abstracts

September 24 – 25, 2024

Agenda

Day 1: Tuesday, September 24, 2024
(All Times Eastern)

11:00 AM – 11:05 AM	**Welcome Remarks and Meeting Objectives** (Zoom) ***Aria Crump***
11:05 AM – 11:55 AM	**IC Directors' Keynote/Fireside Chat** (Zoom) *Moderator:* ***Dr. Marie Bernard*** *Panel Speakers:* • ***Dr. Eliseo Pérez-Stable*** • ***Dr. Wilson Compton*** • ***Dr. Diana Bianchi*** • ***Dr. Jennifer Webster-Cyriaque***
11:55 AM – 12:10 PM	**General Introduction to the NIH Grant and Review Process** ***UnJa Hayes***
12:10 PM – 1:20 PM	**Demystifying NIH Research Funding Opportunities and the Review Process: Concurrent Breakout Sessions by Career Level** (Zoom Breakout Sessions) <u>Breakout: Undergrad/Post-Baccalaureate (1 Room)</u> • ***Anahid Ebrahimi*** • ***Parisa Parsafar*** • ***Erika Barr*** <u>Breakout: Predoctoral Student (6 Rooms)</u> • ***Rob Rivers*** • ***Lauren Ullrich*** • ***Jamie Lahvic*** • ***Lucia Hindorff*** • ***Ashley Smith*** • ***Dave Gutekunst*** <u>Breakout: Postdoctoral Fellow (2 Rooms)</u> • ***Kalynda Gonzales Stokes*** • ***Roya Kalantari*** <u>Breakout: Investigator/Faculty (2 Rooms)</u> • ***Carlos Garrido*** • ***Carolina Solis Sanabria*** <u>Breakout: SBIR/STTR (All Career Levels) (1 Room)</u> • ***Toyin Ajisafe*** • ***Julia Berzhanskaya*** • ***Stephanie Davis***
1:20 PM – 1:40 PM	**Lunch Break** (Zoom or Gather Town Networking)
1:40 PM – 2:15 PM	**Meet with a Program Officer (PO): Small Group Breakout Session with POs from Institutes and Centers** (Gather Town)

2:15 PM – 3:15 PM	**Diversity Supplement Scholar Poster Session A and B** (Gather Town)
3:15 PM – 3:30 PM	**Break**
3:30 PM – 4:45 PM	**A Journey to Becoming an NIH Funded Investigator Panel Discussion** (Zoom) *Moderators:* • ***Houmam Araj*** • ***Toyin Ajisafe*** *Panel Speakers:* • ***Darien Weatherspoon*** • ***Theresa Loveless*** • ***Benga Adeeko*** • ***Jereme Wilroy***
4:45 PM – 4:55 PM	**Entrepreneurial Support and Funding at the NIH** (Zoom) ***Stephanie Fertig***
4:55 PM – 5:00 PM	**Day 1 Closing Remarks/Q&A/Adjourn** (Zoom) ***Marguerite Matthews***

Day 2: Wednesday, September 25, 2024
(All Times Eastern)

11:00 AM – 11:05 AM	**Welcome Remarks** (Zoom) ***Shakira Nelson***
11:05 AM – 11:35 AM	**Keynote Address** (Zoom) ***Arielle Sheftall***
11:35 AM – 12:30 PM	**Get to Know Your NIH Institute/Center** (Zoom Breakout Sessions)
12:30 PM – 1:00 PM	**Lunch Break** (Zoom or Gather Town Networking)
1:00 PM – 2:00 PM	**Diversity Supplement Scholar Poster Session C and D** (Gather Town)
2:00 PM – 2:05 PM	Transition to Zoom
2:05 PM – 3:05 PM	**Resubmissions, Resources, and Resilience (R^3)** (Zoom) • ***Fred Tyson*** • ***Aria Crump*** • ***Lawrence Baizer***
3:05 PM – 3:45 PM	**How to Choose a Mentor and Navigate the Relationship** (Zoom) *Moderators:* • ***Arundhati Gogineni*** • ***Parisa Parsafar*** *Panel Speakers:* • ***Sheryl Frierson*** • ***Dominique Rose*** • ***Deepak Kumar***

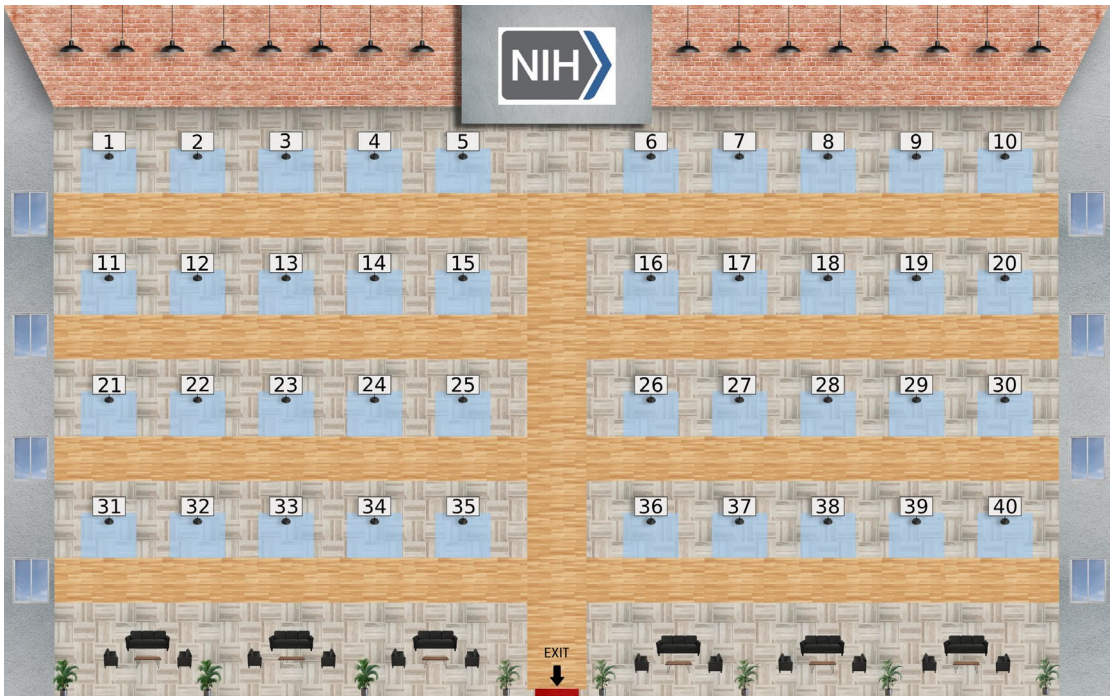
3:45 PM – 4:55 PM	**Science Careers Panel Discussion** (Zoom) *Moderators:* • ***Julia Berzhanskaya*** • ***Utibe Bickham-Wright*** *Panel Speakers:* • ***Rumi Chunara*** • ***Elizabeth Garner*** • ***Kelley Harris*** • ***Marcos Ramos-Benitez***
4:55 PM – 5:00 PM	**Closing Remarks** (Zoom) ***Toyin Ajisafe***

Poster Sessions

Day 1: Tuesday, September 24, 2024

2:15 PM – 3:15 PM

Session A



1 SUV420H2-Mediated H4K20me3 Role in Regulating EMT Plasticity in Breast Cancer
Bachelard Dieujuste, University of Rochester
NCI

2 The Impact of Food Insecurity on Tobacco Use and Cessation Among HIV+ Smokers in Hanoi, Vietnam
Gloria Guevara Alvarez, New York University School of Global Public Health
NCI

3 STAT1 and Guanylate Binding Protein 1 (GBP1) Drive Cell Proliferation in Postpartum Breast Through Downregulation of Cyclin Dependent Kinase Inhibitors: Implications for Increased Postpartum Breast Cancer Risk
Joshua Ogony, Mayo Clinic
NCI

4 Investigating The Role of ADGRB3 Loss of Expression in Brain Tumor Formation in Li-Fraumeni Syndrome
Alex Torrelli-Diljohn, University of Alabama at Birmingham
NCI

5 Examining Disparities in Lung Cancer Risk and Screening Among Individuals with Chronic Obstructive Pulmonary Disorder
Caretia Washington, University of Florida
NCI

6 (Re)Engaging Latino-Led Community-Based Organizations (CBO's) to Build Workforce Capacity in AD/Brain Health Prevention Research
Mirella Diaz-Santos, University of California, Los Angeles/DGSOM
NCATS

7 Altered alveolar cell signature in pre- and post-natal Trisomy 21 lungs
Natalya Cardona Pelayo, University of California, Los Angeles
NHLBI

8 Ultra-low Fouling Anti-infective and Anti-thrombotic Nitric Oxide Releasing Intravascular Catheters
Pravalika Irukulla, Nytricx, Inc.
NHLBI

9 2-Photon Intravital Imaging of Small Diameter Vascular Grafts in an Aortic 3D Culture System
David R. Maestas, Jr., University of Pittsburgh
NHLBI

10 Gasdermin D Promotes Atrial Arrhythmogenesis via Pyroptosis Independent Mechanism
Enrique Martinez, Baylor College of Medicine
NHLBI

11 Restoration of Endothelial Glycocalyx and Reversal of Pro-Atherosclerotic Endothelial Dysfunction with S1P and Heparan Sulfate Derivative Co-Therapy
Kaleigh Pentland, Northeastern University
NHLBI

12 TSLP, IL-4, and IL-13 Increase Transcriptional Programs Associated with Hypercontractility in Human Airway Smooth Muscle
Anushka Ruwanpathirana, The Ohio State University
NHLBI

13 Concordance Between Virtual and Clinical Anthropometric Measures of Children and Adults: A Validity Sub-Study
Jasmin Sanchez, University of Colorado School of Medicine ACCORDS
NHLBI

14 Cholesterol modulation of BK currents and cerebral artery diameter via channel-forming slo1 subunits
Elizabeth Schneider, University of Tennessee Health Science Center
NHLBI

15 Cardiac Fibroblast-MHCII Contribution to Cardiac Pathophysiology in Doxorubicin-Induced Cardiomyopathy
Maria Antonia Zambrano, Tufts University
NHLBI

16 Enhancing Health Equity Through Culturally and Linguistically Tailored Genetics Education Materials
Grace Leon-Lozano, University of North Carolina Chapel Hill
NHGRI

17 Heterogeneity of Preferences for and Outcomes of Pediatric Genomic Sequencing by Race and Ethnicity
Taylor Montgomery, Harvard Pilgrim Health Care Institute
NHGRI

18 Antigen Persistence Following mRNA Vaccination and the Immune Consequence of Lymph Node Stromal Cell Delivery
Robert Belfon, University of Colorado Anschutz Medical Campus
NIAID

19 Expanding the Syphilis Molecular Toolbox: in vitro and in vivo Characterization of Treponema Pallidum Expressing a Constitutive Green Fluorescent Protein Reporter
Kristina Delgado, University of Connecticut Health
NIAID

20 Human DeISGylation Activity Discovered within OTUs from Newly Tamdy Nairovirus of Human Health Concern
David Gonzalez, University of California, Riverside
NIAID

21 CD155-TIGIT-CD226 Mediated Immune Modulation in Tuberculosis Pathogenesis
Louis Hopkins, Emory University
NIAID

22 Correlates of Intestinal Fatty Acid Binding Protein Levels, a Marker for Intestinal Injury, in a Cohort of Kenyan Children under 5 at Hospital Discharge for Non-traumatic Causes
Olivia McCollum, University of Washington
NIAID

23 CMV, Immune Activation, and Mucosal Immunity in Chronic HIV Infection
Ramatoulaye Ouattara, University of California Davis
NIAID

24 The NF-KB Binding Site in the Ifnb1 Promoter is Indispensable for Resistance to Pathogenic Viruses and Defines a Predominant Role of Ifnb1 Over Ifna Genes.
Carolina Rezende Melo da Silva, Thomas Jefferson University
NIAID

25 Investigating the Impact of Tissue Maturity on Cartilage Homeostasis in Inflammatory and Mechanical Stress Conditions
Vianna Martinez, Duke University
NIAMS

26 Monitoring Multiple Sclerosis with IL-23 Responsive Engineered Cells
Gabriela Garza, University of Michigan
NIBIB

27 Characterization of Initial Immune Response by HL-60 Derived Neutrophils and their Role in Host-pathogen Interaction
Anyelo Diaz, University of Massachusetts Lowell
NIDCR

28 One Embryonic rWNT5A Treatment Results in Robinow Syndrome-like Craniofacial Phenotype
Claire Houchen, University of Missouri-Kansas City
NIDCR

29 Porphyromonas Gingivalis Impacts Host Cell Metabolism and Autophagy Pathways in Human Brain Microvascular Endothelial Cells
Brianyell McDaniel Mims, Medical University of South Carolina
NIDCR

30 Antimicrobial Peptide Hydrogel Therapeutic for Apical Periodontitis Treatment
Laura Osorno, New Jersey Institute of Technology
NIDCR

31 APOD Regulates Neural Crest Migration and Otic Placode Specification During Craniofacial Development
Stephanie Peralta, Johns Hopkins University
NIDCR

32 Evaluation of a Training Program for Velopharyngeal MRI
Taylor Snodgrass, East Carolina University
NIDCR

33 Amelogenin (Amelx) Phosphorylation Affects ACP4 Expression
Brent Vasquez, University of Pittsburgh
NIDCR

34 Does Successful Surgical Treatment of Hypernasality Aid in the Remediation of Compensatory Misarticulation Errors?
Jessica Williams, Phoenix Children's Hospital
NIDCR

35 Cholangiocytes' Primary Cilia Regulate DNA Damage Response and Repair
Estanislao Peixoto, Hormel Institute, University of Minnesota
NIDDK

36 Dihydroxyacetone Exposures Induce Genotoxicity and Metabolic Reprogramming in Cardiomyocytes
Hailey Levi, University of Alabama at Birmingham
NIEHS

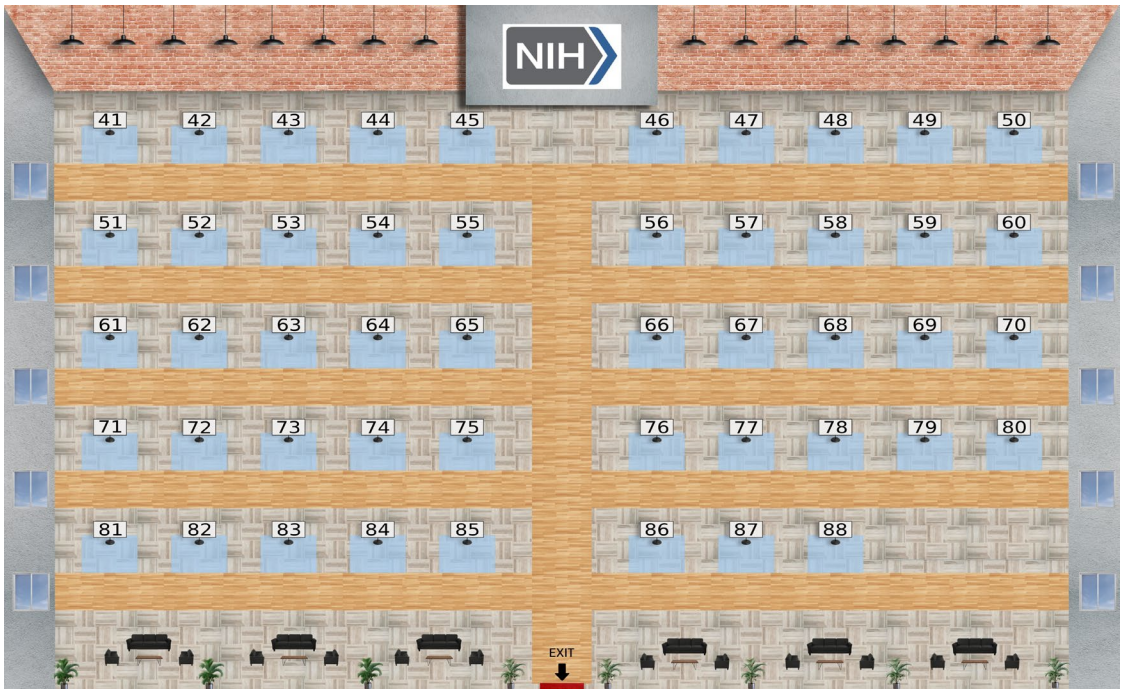
37 Circadian Disruption and EGFR Signaling: Unraveling the Effect of Environmental Chemicals on Placental Extravillous Trophoblast Cell Function
Jacob Moeller, University of Illinois at Chicago
NIEHS

38 The Association of Nursing with Length of Stay for Patients with Intellectual & Developmental Disabilities
Lynne Moronski, University of Pennsylvania
NINR

39 Describing Mexican American Women's Experience of Social Isolation and Discrimination and the Perceived Role of these Stressors on Eating Behavior, Obesity, and Health
Rosario Jaime-Lara, University of California Los Angeles
NIMHD

40 Beliefs about Social Mobility in Young American Children
Tara Mandalaywala, Boston University
NIMHD

Day 1: Tuesday, September 24, 2024
2:15 PM – 3:15 PM
Session B



41 Natural Killer Cells in the Developing Cerebellum: Shepherds or Poachers of Neurogenesis?
Andrew Allee, University of Maryland Baltimore School of Medicine
NIMH

42 The Effects of Reactivation During Sleep on the Neural Representations of Episodic Memories
Sarvia Aquino Argueta, University of California, Irvine
NIMH

43 Resilience and Fatherhood: Exploring Self-Efficacy, Parenting Style, and Mental Health in Post-Conflict Sierra Leone
Abdulai Jawo Bah, Boston College
NIMH

44 iSEE: A Study of the Effects of Structural Inequities and Syndemics on Willingness to Participate in HIV Research among Black Women
Danielle Campbell, University of California, San Diego
NIMH

45 Exploring Acceptability & Potential Reach of Game-Based & Social Network Strategies for Improving PrEP & HIV Self-Testing Uptake among Latinx Men who have Sex with Men Living in an EHE Priority Jurisdiction
Lacey Craker, University of Miami
NIMH

46 Preliminary Data — Family Dynamics and User Engagement in Co-Designing a Mental Health App: A Content Analysis of Satisfaction and Technical Challenges Using ChatGPT
Jacqueline Duong, University of Texas at Austin
NIMH

47 The Coordination of Voltage-Gated Sodium Channels via Ankyrin Protein Interactions
Carina Elvira, University of Michigan - Ann Arbor
NIMH

48 Neurobiology of stress-induced social reward deficits
Rachel Fisher, Icahn School of Medicine at Mount Sinai
NIMH

49 Ketamine Reverses Chronic Stress-Induced Mental Disorders via the Expression of Ca2+-permeable AMPA Receptors in Mice
Joshua Flowers, Colorado State University
NIMH

50 Prenatal Perceptions Mediate Link Between Pregnancy Intention and Caregiver Sensitivity
Juelle Ford, Vanderbilt University
NIMH

51 Associations Between Resting-state Functional Connectivity of the Locus Coeruleus and Anhedonia Symptoms in Individuals with Depression
Gimarie Irizarry-Martinez, University of California, Irvine
NIMH

52 Heterogeneity of Intersectional Discrimination Experiences Among Young Black Gay, Bisexual, and Other Men Who Have Sex with Men in the United States
Sarah Janek, Duke University
NIMH

53 Examining the Relationship between Family Demographics and Engagement with Part C Early Intervention Services across Four US States
Mariela Jiménez, University of Massachusetts Boston
NIMH

54 Diversity of KSHV Subtypes in People Living with HIV in a Large Urban Center in Dallas, Texas
Sheena Knights, University of Texas Southwestern Medical Center
NIMH

55 Increased Anxiety-like Behavior and Stress Responses in Adult Female Rat Offspring of Immune-Activated Dams
Monique Martinez, University of Arizona
NIMH

56 Exploring Determinants of Psychiatric Genetics Research Participation Among Individuals of Latin and African Descent: A Mixed Methods Approach
Ogechi Onyeka, Baylor College of Medicine
NIMH

57 K27 Polyubiquitination is a Sex-specific Regulator of Contextual Fear Memory Formation in the Hippocampus but not the Amygdala
Morgan Patrick, Virginia Tech
NIMH

58 Developmental Shifts in Irritable Behavior Manifestation from Preschool to School-age: A Longitudinal Network Analysis
Erin Peterson, San Diego State University
NIMH

59 Stigma and Sociocultural Variables Related to Latine Adolescents with a History of Suicidal Behavior: Preliminary Qualitative Data
Norka Polanco- Frontera, Ponce Health Science University
NIMH

60 Effects of Recruitment Messaging on Ethnic/Racial Minority Enrollment in an RCT for Prenatal Insomnia: An Experimental Approach
Carolyn Ponting, University of California, San Francisco
NIMH

61 Prenatal Substance Use During the COVID-19 Pandemic: Exploratory Analyses
Marco Ramirez Gonzalez, Washington State University
NIMH

62 Exploring PrEP Stigma Homophily and PrEP Conversations Among Latinx Men Who Have Sex With Men (LMSM) in South Florida
Edda Rodriguez, University of Miami
NIMH

63 Ethical Considerations of Data Sharing Policies in Neuroscience Research: A Case Study on Data Sharing Practices in Autism Research
Zuzana Skvarkova, Baylor College of Medicine
NIMH

64 Exploring the socio-ecological environment on the Malkia Klabu program for adolescent girls and young women in Tanzania
Camila Solorzano Barrera, University of California San Francisco
NIMH

65 Higher Inflammatory Proteins Predict Future Depressive Symptom Severity Among Adolescents with Lower Emotional Clarity
Auburn Stephenson, Temple University
NIMH

66 Whose Depression are We Measuring? A Holistic Approach to Understanding Black Women's Health
Kanetha Wilson, Kaiser Permanente Georgia, Center for Research and Evaluation
NIMH

67 Functional Characterization of Ultraconserved Elements in Neuronal Cell Types: Investigating Enhancer Activity and Cell-Specific Gene Regulation Using CRISPRi
Mark Youssef, Mount Sinai and Icahn School of Medicine
NIMH

68 Neural Mechanism of Prism Adaptation Therapy is Enhanced with Electrical Stimulation
Fisayo Aloba, Emory University
NINDS

69 A Vault Bionanoparticle-Encapsulated Frataxin Gene-Targeted Histone Demethylation for Contracting GAA Repeats in Friedreich's Ataxia
Rhyisa Armbrister, Florida International University
NINDS

70 Exploring the Pathophysiology of Cognitive Dysfunction after Combination of Traumatic Brain Injury and Cortical Spreading Depolarization
C'Asia Bishop, University of Cincinnati
NINDS

71 Associations Between Perinatal HIV-related Risk Factors and Select Serum Polyunsaturated Fatty acid (PUFA) Levels Among Ugandan Children and Adolescents
Vanessa Cardino, Michigan State University
NINDS

72 Postnatal Development of Vasculature in the Hippocampal Neural Stem Cell Niche
India Carter, The Ohio State University
NINDS

73 Elucidating the Role of Reactive Astrocytes on the Modulation of Blood-brain Barrier Dynamics through the STAT3-SERPINA3 Signaling Axis in Alzheimer's Disease
Rebecca Embalabala, Vanderbilt University
NINDS

74 Investigating Dynamics of Astrocyte Endfoot Formation During Development and Across Species
Raja Estes, Oregon Health & Sciences University
NINDS

75 Exploring Heterochromatin Alterations as a C9orf72 FTD/ALS Hallmark
Raven Fisher, The Graduate Center of the City University of New York
NINDS

76 Interference Between Similar Memories Increases the Dimensionality and Dispersion of Recalled Content
Julian Gamez, University of Oregon
NINDS

77 Loss of m6A mRNA Readers in Zebrafish Model Impacts Brain Size Phenotypes Implicated in Autism
Gabriana La, University of California, Davis
NINDS

78 L-selectin Shedding Regulates Neutrophil Function in a Sex-dependent Manner After Spinal Cord Injury
Miranda Leal-Garcia, Texas A&M University
NINDS

79 Computational Modeling of Platelets and Thrombosis in Cerebral Aneurysm Treatment
Do Lim, University of Washington
NINDS

80 Mice Sleep Less During the Wake Cycle After Repeated Closed Head Injury
Kyli McQueen, University of Arizona College of Medicine - Phoenix
NINDS

81 The Impact of Increased Blood Pressure Variability and High Salt Diet on Cardiovascular and Neurovascular Outcomes
Perenkita Mendiola, Augusta University
NINDS

82 Elucidating the Role of Vagal Signaling in CNS Reward Networks
Chris Phillips, University of Texas at Dallas
NINDS

83 Mitochondrial Network Dynamics During Microglia Surveillance and Phagocytosis
Alicia Pietramale, Dartmouth College
NINDS

84 Multi-omics Analyses and Functional Synaptome Aberrations in C9orf72 ALS/FTD
Ashton Spillman, Barrow Neurological Institute
NINDS

85 Non-canonical Roles of Cell Adhesion Molecules in Presynaptic Patterning
Jada Summerville, Albert Einstein College of Medicine
NINDS

86 Kilohertz Transcranial Magnetic Perturbation (kTMP): A New Subthreshold Method to Modulate Cortical Excitability
Katheryn Thayer-Pham, University of California, Berkeley
NINDS

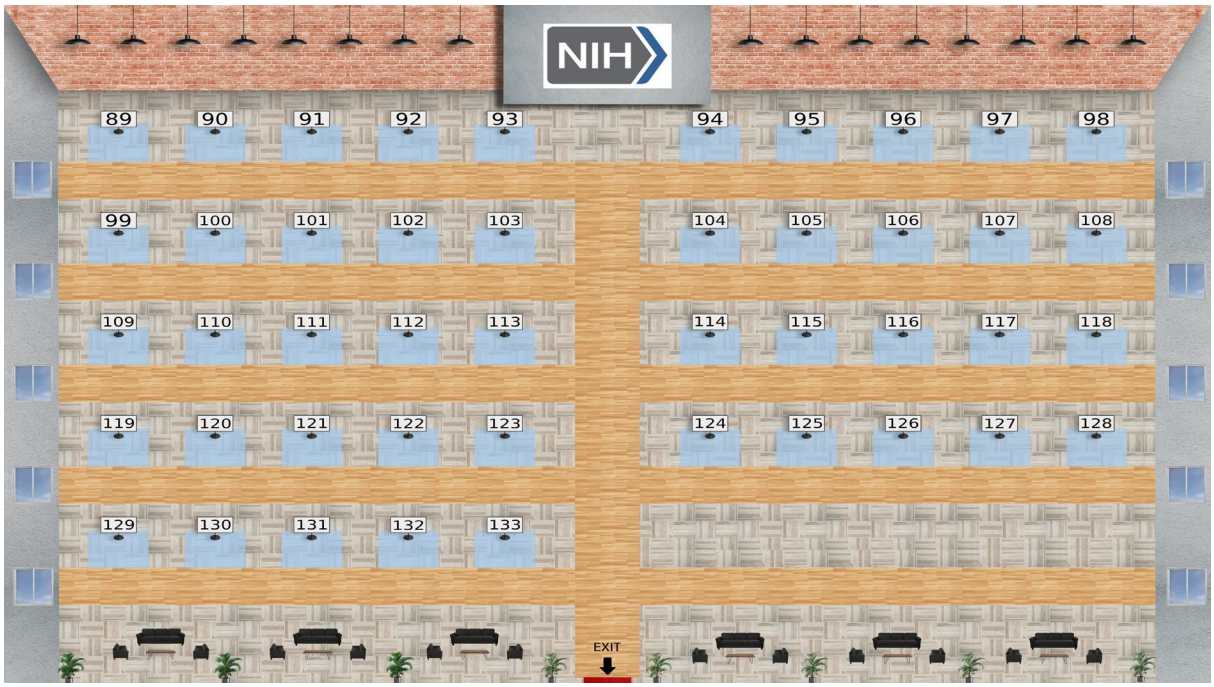
87 Microglia Depletion Reduces CD8+ T-cell Infiltration into the Injured Brain in Aged Mice After Traumatic Brain Injury
Veronica Villanueva, Northwestern University
NINDS

88 Scn2a Haploinsufficiency Leads to Absence-type Seizures in a Sex-dependent Manner
Vivianna DeNittis, Gladstone Institutes/UCSF
NINDS

Day 2: Wednesday, September 25, 2024

1:00 PM – 2:00 PM

Session C



89 Usability Testing of the HOPE App Platform: An Immersive Telehealth Solution for Older Adults with Diabetes
Gifty Asante, See Yourself Health
NIA

90 Supportive Language Patterns in Stroke Caregiver-Patient Dyads: Initial Observations
Fedora Biney, University of Alabama at Birmingham
NIA

91 Behavioral Analysis Using DeepLabCut & Keypoint-MoSeq
Mary Cooper, University of Alabama at Birmingham
NIA

92 A Study of Racial and Ethnic Differences in Willingness to Participate in Preclinical AD Trials
Edwin Duran, University of California Irvine Institute for Memory Impairments and Neurological Disorders
NIA

93 Sex Differences in the Response to High Pulse Pressure
Skylyn Ferguson, University of Oregon
NIA

94 Impacts of Informant Replacement in Global Industry-Sponsored Alzheimer's Disease Clinical Trials
Mikaela Nishida, University of California, Irvine
NIA

95 Improving Study Recruitment of Older Adult Patients
J'Heannhehbelle Rosier, University of Chicago
NIA

96 Exploring Care Transition Experiences of Hispanic Patients with Dementia Following Emergency Department Discharge: A Dyadic Qualitative Study
Jacqueline Sandoval, Yale University
NIA

97 Faster DunedinPACE, an epigenetic clock for pace of biological aging, is associated with accelerated cognitive aging among older adults in the Framingham Heart Study
Micah Savin, Columbia University
NIA

98 Assessment of the Association of Eicosanoids with Incident Stroke Over Decades in the Atherosclerosis Risk in Communities (ARIC) Study
Alexis Simpkins, Cedars-Sinai Medical Center
NIA

99 Associations Between Emotion Regulation and Mental Health Among Dementia Caregivers Across Time
Anna Toledo, Georgetown University
NIA

100 Can’t Get No Satisfaction: Developing a Fly Model of Hedonic Tolerance
Pearl Cummins-Beebee, University of Utah
NIAAA

101 Assessing the Effects of Prenatal Cannabinoid Consumption on Fetal Brain Vasculature Utilizing Optical Coherence Angiography
Jessica Gutierrez, University of Houston
NIAAA

102 Addressing Structural Disparities for Children with Early Communication Disorders Diversity Supplement
Joshuaa Allison-Burbank, Johns Hopkins University
NIDCD

103 The Role of Nonverbal Communication in Autistic Gender-Diverse Adults' Everyday Lives
Maci Brown, Drexel University
NIDCD

104 Mitochondrial Dysfunction in the Aging Inner Ear's Cellular Battery
Tyreek Jenkins, Medical University of South Carolina
NIDCD

105 Does Prosodic Richness Impact Spoken Emotion Identification?
Devon Major, Boys Town National Research Hospital
NIDCD

106 Dynamics of Emotion Processing in Post-stroke Aphasia: Insights From Continuous Valence Ratings During Naturalistic Movie-viewing
Manuel Marte, Boston University
NIDCD

107 The Interaction of Language, Executive Functioning, and Structured Physical Activity for Children with Down Syndrome
Jessica Mattingly, Boys Town National Research Hospital
NIDCD

108 Identifying the Mechanisms of Astringency Transduction
Mikaéla Murph, New York University College of Dentistry
NIDCD

109 Anatomy of Tongue-Innervating Mechanoreceptors
Thomas Myers, University of Louisville
NIDCD

110 Psycholinguistic Effects on Silent Reading Comprehension Accuracy in Aphasia-based Alexia
Candace van der Stelt, University of Pittsburgh
NIDCD

111 Reexamining Taste Cell Lifespan Using in vivo Two-photon Laser Scanning Microscopy
Brittany Walters, University of Louisville School of Medicine
NIDCD

112 Age- and Sex-Specific Effects of Oxycodone Self-Administration during Gestation on Offspring Reward Motivation
Chantal Aaron, Tufts University
NIDA

113 Experiences of Substance Use and Medication for Opioid Use Disorder Stigmas in an Underserved, Rural Community
Morgan Anvari, University of Maryland
NIDA

114 Planned Use of Medication for Opioid Use Disorder Among Adolescents Entering Treatment for Opioid Use Disorder and Trends in the US, 2017-2021
Jesse Boggis, Geisel School of Medicine at Dartmouth
NIDA

115 A Preliminary Investigation of a Community-Based Participatory Research Approach to Recovery Capital Measures for Emerging Adults (Ages 18-25)
Eden Buell, Chestnut Health Systems- Lighthouse Institute
NIDA

116 Community Social Relations and Their Impact on Black and Latine Peoples' Substance Use Recovery Journey
Mark Costa, Yale School of Medicine
NIDA

117 The Moderating Role of Pubertal Development in the Association Between Subjective Socioeconomic Status and Future Career Orientation
Avary Evans, University of Georgia
NIDA

118 Characterization of Nicotine Withdrawal Severity Across the Estrous Cycle in Female Rats
Priscilla Giner, The University of Texas at El Paso
NIDA

119 Social Determinants of Health for Predicting Risks of HCV Infection and HCV/HIV Co-infection
Pilar Hernandez Con, University of Florida
NIDA

120 Exploring the Accessibility, Acceptability, and Utilization of a Community-based Harm Reduction Vending Machine Among Persons with Limited Opportunity Structures
Ashleigh Herrera, California State University Bakersfield
NIDA

121 Diurnal Rhythms in Striatal Acetylcholine and Dopamine Dynamics are Modulated by Differential Cocaine Access
Melody Iacino, Wake Forest University
NIDA

122 L-type Calcium Channel Blockade Selectively Attenuates Cue-induced Cocaine-seeking in Female Rats
Violet Kimble, Yale University
NIDA

123 Characterizing NTSR1-expressing Medial Prefrontal Cortex Afferents into the Nucleus Accumbens in the Context of Opioid-seeking
Crystal Lemchi, University of Minnesota
NIDA

124 Barriers to Mental Health Services in Emerging and Early Adulthood: A 16-Year Longitudinal Study of Youth After Juvenile Detention
Maria Jose, Luna, Northwestern University Feinberg School of Medicine
NIDA

125 Effect of Oxytocin on Hyperalgesia in Alcohol-Dependent Rats
John, Marendes Jr., University of Tennessee Health Science Center
NIDA

126 Age-Varying Patterns of Substance Use from Early Adolescence to Young Adulthood Among Latinx Individuals Growing up in Rural or Small-Town Communities in the U.S.
Griselda Martinez, University of Washington
NIDA

127 Self-selected Edible Cannabis Products for Chronic Low Back Pain: Outcomes on Pain, Mood, and Intoxication Effects
Samantha Melendez, University of Colorado Boulder
NIDA

128 Factors Influencing Rapid ART and HIV Care Engagement Among Young Black and Latinx Sexual and Gender Minorities with HIV
Ofole Mgbako, New York University Grossman School of Medicine
NIDA

129 Cortical Astrocytes Sex-Specifically Modulate EcoHIV-Induced Extinction Learning Impairments
Mark Namba, Drexel University College of Medicine
NIDA

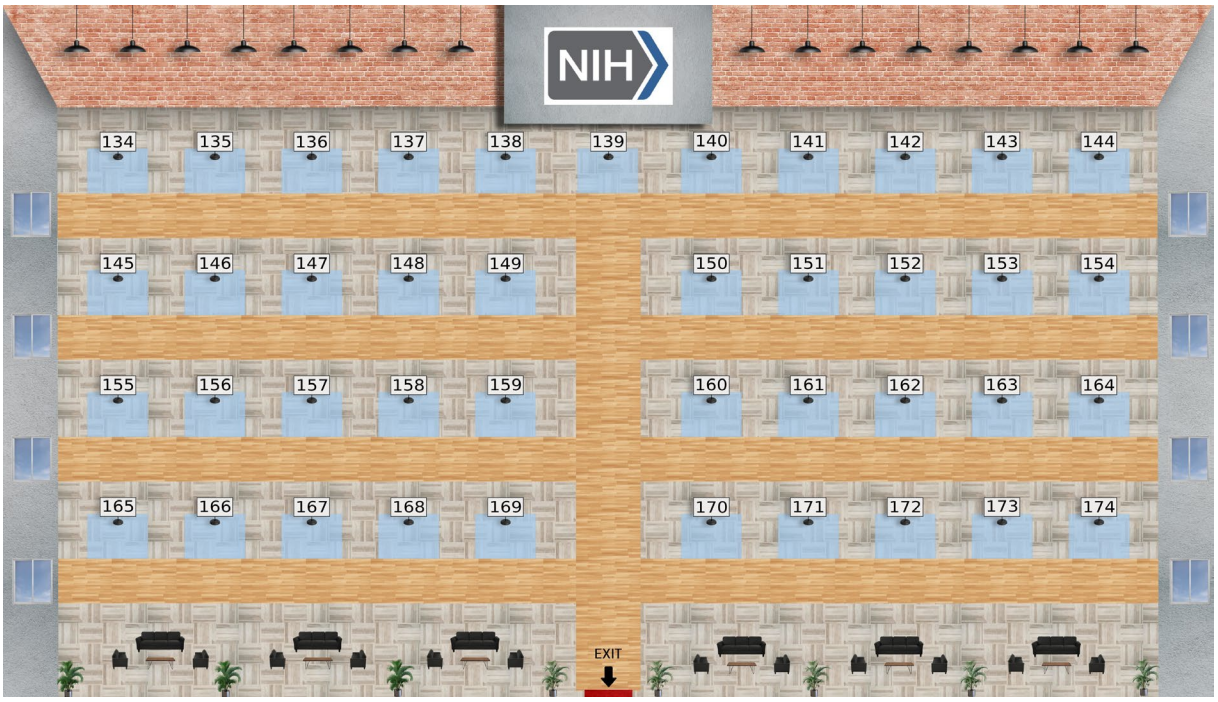
130 Association between Heightened Vigilance and Cannabis Use Disorder Severity
Emma Quarles, Virginia State University
NIDA

131 Cumulative Lifetime Stress Exposure is Differentially Related to Ambiguity Attitudes in a Clinical Population with Opioid Use Disorder
Joshua Stuckey, Rutgers University
NIDA

132 Replication of Hallucination Severity Associating with Reduced Auditory-language Cortex Connectivity in a Biological Subtype of Psychotic Disorders
Isaac Toscano, University of Chicago
NIDA

133 Maternal Incarceration and Adolescent Girls' Risk of Substance-exposed Pregnancy, STIs, and HIV
Qianwei Zhao, Baylor University
NIDA

Day 2: Wednesday, September 25, 2024
1:00 PM – 2:00 PM
Session D



134 Automated Quantifiable Assessments of Sensorimotor Function Using an Instrumented Fragile Object
Michael Adkins, University of Utah
NICHD

135 Understanding the Associations Between Hand Muscle Motor Evoked Potentials and Motor Function in Stroke Survivors
Jenna Blaschke, Medical University of South Carolina
NICHD

136 VGLL1-mediates Crosstalk of BMP, HIPPO, and WNT Signaling Pathways During Human Trophectoderm Specification
Ruben Calderon, University of California San Diego
NICHD

137 Macrophage Signatures and Dynamics in the Mouse Postpartum Uterus
Maria Natalia Chaves Rivera, Yale University School of Medicine
NICHD

138 Assessing the Perinatal Outcomes and Needs of Women on Probation
Allison Crawford, University of Texas Health at San Antonio
NICHD

139 Acetaminophen Induced Toxicity in Lung Epithelial Cells is Cyp2e1 Dependent
Lily Emmanuel, University of Colorado Anschutz Medical Campus
NICHD

140 A Prostate Specific Antigen (PSA) Inhibitor Shows Potential for a Non-Hormonal Contraceptive Method
Jeffery Erickson, University of Missouri - Columbia
NICHD

141 Home Task Practices Increase Stroke Survivors' Real-World Upper Limb Use as Measured by Wearable Accelerometer
Ja'Quann Gallant, Medical University of South Carolina
NICHD

142 Development of Acoustic Startle Response and Prepulse Inhibition in Fragile X Syndrome Mice
Andrea Gensky, Oklahoma State University
NICHD

143 Impact of PBDE-47 Exposure on Placental Immune Tolerance Mediated by Extracellular Vesicle miRNA-519c
Rahanna Khan, New York University Grossman School of Medicine
NICHD

144 Closing the Gaps: Racial and Ethnic Disparities in Traumatic Childbirth and Co-Morbid Conditions
Kelimer Lebron-Sagardia, Massachusetts General Hospital & Harvard Medical School
NICHD

145 Characterizing Non-PRC2 Catalyzed Histone H3K27me3 in Transcriptional Regulation
Itzaira Mercado Hernandez, University of Michigan
NICHD

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Poster Abstracts

SUV420H2-Mediated H4K20me3 Role in Regulating EMT Plasticity in Breast Cancer

Bachelard Dieujuste, University of Rochester
NCI
Poster 1
bachelard_dieujuste@urmc.rochester.edu

Breast cancer is the most common cancer diagnosed in women and the leading cause of mortality. This mortality is often due to metastasis, a phenomenon where tumor cells disseminate throughout the body. One factor contributing to the ability of cancer cells to progress to this stage is the epithelial-to-mesenchymal transition (EMT), a reversible state of cellular plasticity in which epithelial cells lose cell-to-cell adhesion and gain migratory and invasive properties. While EMT is thought to promote the early stages of metastasis, growth at the distant site requires the retention/re-acquisition of epithelial characteristics. This plasticity in cell states is mediated by epigenetic factors that control the openness of chromatin for gene expression. In that regard, our lab and others found that downregulation or inhibition of SUV420H2, a histone methyltransferase that is responsible for tri-methylating lysine 20 of histone H4 (H4K20), a mark typically associated with repression, promotes EMT in breast epithelial cells. These data suggest that SUV420H2 suppresses EMT and plays a role in mediating the epithelial vs. mesenchymal identity. To study the role of SUV420H2 and H4K20me3 in EMT/mesenchymal epithelial transition (MET) plasticity, I am using a model in which plasticity is induced by transforming growth factor-β (TGF-β), a growth factor in the microenvironment. In normal and early breast cancer tissues, TGF-β acts as a tumor suppressor by limiting cell proliferation. However, as cancer progresses, TGF-β promotes tumor progression in part by driving EMT. Using MCF10A immortalized breast epithelial cells, and a recovery and re-challenge approach, I have defined the reversibility of TGF-β-induced EMT. I found that, upon TGF-β treatment, MCF10A cells lose their cuboidal shape during which they gain a spindle shape, which is lost upon recovery. However, upon TGF-β-re-challenge, mesenchymal marker genes are super-induced in comparison to the first treatment, and cells regain their spindle shape. These data suggest that there is a 'memory' or an imprint of prior exposure that influences future gene regulation. We also performed CUT&Tag to determine the impact of TGF-β on H4K20me3. We found that, following TGF-β treatment, H4K20me3 accumulates at several hundred base pair away from the transcription start sites (TSS) across the genome. Future studies will address the mechanism by which TGF-β signaling triggers localization of SUV420H2 and the role of H4K20me3 at these sites is unknown. Overall, the results of this study will help define the role of TGF-β -induced H4K20me3 in regulating EMT plasticity and provide insight to better target epigenetic modifiers to prevent breast cancer progression.

The Impact of Food Insecurity on Tobacco Use and Cessation Among HIV+ Smokers in Hanoi, Vietnam

Gloria Guevara Alvarez, New York University School of Global Public Health
NCI
Poster 2
gga2009@nyu.edu

Background: Smoking causes disparate health outcomes among people living with HIV (PWH). PWH also experiences higher rates of food insecurity (FI) compared to HIV-negative adults. Additionally, HIV and smoking are independently associated with FI. In low resource settings with heavy burdens of HIV and tobacco use, FI is especially prevalent, but these overlapping conditions are understudied, particularly in low-to-middle-income countries (LMICs), where the majority of PWH live. Our study aimed to understand the relationship between FI and tobacco use among PWH.

Methods: We used a longitudinal survey design, nested within an ongoing randomized controlled trial (RCT) focused on tobacco use treatment. Between November 2021 and June 2022, we surveyed 182 HIV+ smokers receiving care at five HIV clinics in Hanoi, Vietnam. We measured FI and tested associations between FI and social demographics, and tobacco dependence and readiness to quit.

Results: Prevalence of FI among at baseline was 13.3%. Living alone [RR 2.85 (CI:1.08, 7.52); p = <0.001)], years living with HIV [RR 1.40 (CI: 1.13, 1.74); p = 0.025], and having a lower income (20% versus 3.8% as compared to having mild-to-little FI; p = 0.01) were associated with an increase in moderate-to-severe FI. Among participants who experienced moderate-to-severe food FI at baseline, adjusted logistic regression revealed: a significant positive association of moderate-to-severe FI with high tobacco dependence (RR 1.48; p = 0.01), p = 0.05; higher drug use [RR 0.84 (CI: 0.73, 0.96) p = 0.004], and clinically significant depression (RR -1.43; p = 0.05); and a negative association with FI Readiness to quit (6.73% versus 93.27%) [(RR -1.39; p = 0.01) p = 0.001].

Conclusion: FI is associated with higher rates of depression and drug use, both of which are modifiers of smoking, and higher rates of tobacco addiction and lower rates of readiness to quit, which are strongly tied to tobacco cessation. Understanding how FI interacts with these factors may inform barriers to cessation and help to adapt tobacco use treatment for PWH who are food insecure, mitigating this common triple burden in LMICs.

STAT1 and Guanylate Binding Protein 1 (GBP1) Drive Cell Proliferation in Postpartum Breast through Downregulation of Cyclin Dependent Kinase Inhibitors: Implications for Increased Postpartum Breast Cancer Risk

Joshua Ogony Mayo Clinic
NCI
Poster 3
ogony.joshua@mayo.edu

Postpartum breast cancer (PPBC) is a highly aggressive form of breast cancer that significantly increases in risk within 5 to 10 years after childbirth. To define molecular mechanisms underlying this elevated risk, we compared breast tissue samples from 5 postpartum women within five years of a last childbirth to those from 5 age- and BMI-matched nulliparous women. Transcriptomic profiling of breast tissues revealed significant upregulation of interferon-stimulated genes STAT1 and GBP1, consistent with previous studies showing increased immune response in postpartum tissues. Further analysis showed increased expression of the proliferation marker Ki67 and enrichment of cyclins and cyclin-dependent kinases and downregulation of their inhibitors, suggesting a heightened proliferation phenotype in postpartum tissues. Immunohistochemistry confirmed increased expression of Ki67, STAT1, and GBP1 in postpartum breast epithelial cells. To explore these findings functionally, human mammary epithelial cells (HMECs) were isolated from breast tissue fragments, and STAT1 and GBP1 were silenced. Knockdown of these genes resulted in decreased cell proliferation, G1 cell circle arrest, and increased expression of CDKN1A and CDKN1C. These results indicate that STAT1 and GBP1 drive a proliferative phenotype in postpartum breast tissue, potentially contributing to the increased risk of PPBC. This study identifies novel molecular targets for understanding and potentially mitigating postpartum breast cancer risk.

Investigating The Role of ADGRB3 Loss of Expression in Brain Tumor Formation in Li-Fraumeni Syndrome

Alex Torrelli-Diljohn, University of Alabama at Birmingham
NCI
Poster 4
torrelli@uab.edu

Authors: Alex Torrelli-Diljohn (1); Benjamin Lin (2); Shaurita Hutchins (1,3); Abigail Shelton (1,5); Ryan Bash (3); Svetlana Komarova (3); Vipul Sheth (2); Paran Goel (4); Robert Welner (4); Jeremy Foote (4); David Crossman (3); Ryan Miller (5); and Erwin G. Van Meir (3)

Institutions:
1. Pharmacology, Physiology, & Pathobiology Theme, University of Alabama at Birmingham
2. Department of Neurosurgery, University of Alabama at Birmingham
3. Department of Pathology, University of Alabama at Birmingham
4. Hematology-Oncology, University of Alabama at Birmingham
5. Department of Genetics, University of Alabama at Birmingham

Li-Fraumeni syndrome (LFS) is a rare cancer predisposition syndrome caused by a germline mutation in the TP53 tumor suppressor gene. Glioblastoma (GBM) is the most prevalent central nervous system tumor in LFS, with TP53 mutations detected in 30% of sporadic GBMs. GBM is the most aggressive primary brain neoplasm that affects adults, with a median survival of 12-15 months. Recent studies implicate the dysregulation of adhesion G-Protein coupled receptors (GPCRs) in GBM development. Brain angiogenesis inhibitor 3 (BAI3/ADGRB3), a member of the BAI1-3 subfamily of adhesion GPCRS, has been observed to have low expression in brain tumors according to TCGA data, but the significance of this observation has not been explored. However, while its sister protein BAI1 has demonstrated tumor suppressor functions in the brain, it remains unclear whether BAI3 shares this role. To test this, an LFS mouse model (germline Tp53 deletion) with a second floxed allele under the control of Nestin-Cre was crossed to Bai3-/- mice. Preliminary findings indicate that the simultaneous loss of Bai3 and Tp53 expression in our mouse model increased spontaneous brain tumor formation incidence from 34% to 71%, in contrast to the loss of p53 alone. These observations lead me to hypothesize that ADGRB3 functions as a tumor suppressor in the brain, and its silencing, in the context of p53 mutation, facilitates GBM formation. Isolated GBM stem cells were collected for further genomic analyses and to test whether overexpression of BAI3 will save the tumor phenotype.

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Examining Disparities in Lung Cancer Risk and Screening Among Individuals with Chronic Obstructive Pulmonary Disorder

Caretia Washington, University of Florida
NCI
Poster 5
caretia.washingt@ufl.edu

Background: Lung cancer is the leading cause of cancer-related deaths globally and in the U.S. Despite the potential of Low-Dose Computed Tomography (LDCT) to reduce lung cancer mortality, only 5.8% of eligible individuals undergo lung cancer screening (LCS). Various factors, including socioeconomic status, healthcare access, and comorbid medical conditions, contribute to the low uptake of LCS. Chronic Obstructive Pulmonary Disorder (COPD), a common comorbidity among individuals undergoing LCS, impacts the benefit-harm ratio of screening. Additionally, racial disparities exist in LCS utilization, COPD severity, and lung cancer survival.

Objective: This study aims to assess the utilization of lung cancer screening among individuals with COPD and identify disparities in screening rates by race and ethnicity.

Methods: We will analyze data from 60,251 patients with COPD in the OneFlorida Database, evaluating lung cancer risk, LCS utilization, and screening outcomes by race and ethnicity.

Conclusions: Preliminary findings indicate a higher comorbidity burden among Black individuals with COPD, correlating with increased lung cancer risk. However, only 5% of COPD patients receive LCS. Future work will involve cluster analysis to identify COPD clinical phenotypes and further assess demographic factors such as rurality and socioeconomic status.

This study seeks to highlight disparities in LCS utilization, ultimately guiding interventions to improve screening rates among high-risk populations.

(Re)Engaging Latino-Led Community-Based Organizations (CBO's) to Build Workforce Capacity in AD/Brain Health Prevention Research

Mirella Diaz-Santos, University of California, Los Angeles/DGSOM
NCATS
Poster 6
mdiazs antos@mednet.ucla.edu

Background: AD prevention and early detection are crucial to reducing prevalence projections in Latinos. Despite these projections, our community partners in Los Angeles County continue to disclose barriers in accessing culturally and linguistically congruent bilingual programs activating behavioral modifications for AD prevention and early identification of cognitive changes. In this study, we partnered with community organizations to co-design and pilot a brain health prevention program tailored to the needs of their constituents.

Methods: We used a mixed-methods design using quantitative data from surveys, and qualitative data from informal short interviews in Spanish and English with Latino community organizations and their constituents. We implemented Community-Based Participatory Research (CBPR) and Human Centered Design (HCD) principles, anchoring the program in the cognitive reserve theory, tailored to cultural values, traditions, and needs of Latinos in Los Angeles County. Spanish and English-speaking Latino members requested brain health and early detections materials easy to comprehend. Four Spanish and English brochures were designed. We also designed a communication training toolkit to improve delivery of the program from our research team, employing oral storytelling techniques with cultural metaphors explaining brain structure/functions and cognitive functioning/decline.

Results: Between June and December 2023, our team received invitations to participate in 11 community engagement and outreach events across Los Angeles County. A team of 3 bilingual trained research assistants engaged with approximately 475 Spanish- and English-speaking community members with an average of 43 individuals per event. Distance traveled averaged 37 miles roundtrip total per event. Total printing cost per event was approximately $292, with an additional $30 for giveaways. In the 6 months of implementation, a total of 30 community-based organizations requested formal presentations and trainings for their staff. Overarching qualitative themes included the community-centeredness of the program; it's cultural, linguistically and health literacy appropriateness; and the culturally competent communication skills showcased by bilingual research staff.

Conclusion: Following CBPR and HCD principles, we showed respect for community needs while empowering the members to be an integral part of the design and pilot. Our approach engaged and recruited 30 Latino-led community organizations interested in building their own workforce capacity in brain health prevention and early detection.

Altered Alveolar Cell Signature in Pre- and Post-natal Trisomy 21 Lungs

Natalya Cardona Pelayo, University of California, Los Angeles
NHLBI
Poster 7
ncardonacastillo1@toromail.csudh.edu

Rationale: Pulmonary and cardiovascular disorders result in 75% of the mortality observed in individuals with Down Syndrome (DS). However, little is known about the pulmonary anomalies observed in DS, as they are often considered a secondary condition to congenital heart defects. However, we and others have demonstrated that lungs from patients with trisomy 21 (T21) may present
alveolar abnormalities, such as pulmonary alveolar hypoplasia, regardless of congenital heart disease. Therefore, the etiology of alveolar defects in T21 lungs remains elusive. The aim of our study is to define the molecular and cellular defects underlying alveolar defects in T21 developing lungs.

Methods: Single cell RNA sequencing data was generated from 5 T21 and 4 non-T21 human fetal lungs
(18 weeks gestation). T21 and non-T21 human fetal lung tissues (aged 18 to 22 weeks gestation), and postnatal human lung tissues from 2 months to 6 years old were processed to compare and determine the localization and expression of cells and their markers by RT-qPCR, fluorescence in situ hybridization (FISH) and immunofluorescent staining (IF).

Results: Our single cell data showed an increase in the proportion of mature fetal AT2 cells in T21 as compared to non-T21 samples, whereas a decrease was observed in the intermediate and progenitor cell populations. When comparing fetal T21 to non-T21 samples, RT-qPCR results demonstrated increased expression of both alveolar type II markers (SFTPD, ABCA3, LAMP3) and the alveolar type I marker AGER. Furthermore, FISH showed a significant increase in SFTPC and SFTPB in fetal T21 lungs. Conversely, when comparing postnatal T21 to non-T21 samples, RT-qPCR results demonstrated reduced expression of alveolar type II markers (ABCA3, SCGB3A2) and alveolar type I markers (HOPX, AGER, PODOPLANIN). Our IF staining in postnatal T21 vs non-T21 showed a significant increase in the number KRT8 and KRT8+/SFTPC+ cells, markers of an intermediate progenitor cell population, accompanied by a decrease in proliferating AT2 cells (SFTPC+/Ki67+).

Conclusion: While our single cell data, RT-qPCR, FISH and IF results show an accelerated maturation during T21 lung fetal pre-alveolar development, postnatal T21 lungs display a decrease in mature AT2 cell numbers. This could likely be due to an accelerated maturation early on in development, that suppresses proper proliferation necessary to expand the pool of AT2 cells to a normal range. This suppression seems to persist into the postnatal period.

Ultra-low Fouling Anti-infective and Anti-thrombotic Nitric Oxide Releasing Intravascular Catheters

Pravalika Irukulla, Nytricx, Inc.
NHLBI
Poster 8
pirukulla@nytricx.com

Intravascular catheters are widely used for patient treatment and diagnosis, particularly in intensive care units. In the US alone, more than 330 million peripheral catheters are used annually, affecting more than 70% of hospitalized patients. However, indwelling vascular catheters are susceptible to two primary complications: (1) thrombosis (blood clots) and (2) infections occurring after insertion. Thus, there is an unmet medical need for antifouling, non-thrombogenic, and antimicrobial catheters. Nytricx is addressing this need by incorporating the Nitric Oxide (NO) donor, S-Nitroso-N-acetylpenicillamine (SNAP), into silicone catheters which provide antimicrobial and anti-thrombotic effects through sustained and controlled release of gaseous NO. Additionally, Nytricx is applying a liquid silicone oil topcoat to create a super slippery surface to prevent bacterial adhesion and surface fouling. Thus, Nytricx is developing an intravascular Liquid-Infused Nitric Oxide Releasing (LINORelTM) catheter that releases antimicrobial and antithrombotic NO. Further, NO has not been associated with antibiotic resistance which is a major problem with marketed antibiotics.

LINORelTM catheters were developed using a dip coating method on stainless steel mandrels and infused with silicone oil (100 cSt) for 6h. The catheters were then evaluated for NO release, antimicrobial and anti-thrombotic activity over a 28-day period. The LINORelTM catheters demonstrated sustained NO release at physiologically relevant levels (0.5-4 x 10-10 mol min-1 cm-2) and demonstrated a significant reduction in bacterial adhesion and blood clot formation on the catheter surface.

This study highlights the novel combination of NO release with liquid infusion of silicone oil to enhance the antimicrobial and anti-thrombotic properties of intravascular catheters. Additionally, Nytricx is currently reinforcing NO-releasing silicone catheters with nylon to enhance the structural integrity of the catheters for high pressure diagnostic CT testing.

2-Photon Intravital Imaging of Small Diameter Vascular Grafts in an Aortic 3D Culture System

David R. Maestas, Jr., University of Pittsburgh
NHLBI
Poster 9
drm154@pitt.edu

The development of tissue engineered vascular grafts (TEVGs) has seen major advancements in the past few decades, yet one of the most challenging aspects of these grafts is the requirement for them to be tested in animal models. This requires sufficient funding, surgical skill, and diligent post-surgical animal care. Further, small surgical errors or differences in techniques may confound which outcomes arise from the graft vs the implantation process. In this work, we developed a 3D culture system that utilizes explanted rat aortas canulated to small diameter TEVGs, and assessed extracellular matrix remodeling upon the TEVGs with non-destructive intravital 2-photon imaging. This new culture system provides an advanced platform to more rapidly assess specific aspects of TEVG biocompatibility before implantation into model animals.

Gasdermin D Promotes Atrial Arrhythmogenesis via Pyroptosis Independent Mechanism

Enrique Martinez, Baylor College of Medicine
NHLBI
Poster 10
enrique.martinez@bcm.edu

Authors: Enrique Martinez, BS1,2, Yue Yuan, MD, PhD1,2, Xiaohui Chen, PhD1,2, Pacal Martsch, PhD3, Jia Song, MD, MS1,2, Luge Li, BS1,2, Florian Bruns, MD3, Issam Abu-Taha, PhD3, Dobromir Dobrev, MD3, Na Li, PhD1,2

Affiliations:
1. Departments of Medicine (Cardiovascular Research)
2. Cardiovascular Research Institute, Baylor College of Medicine, Houston, TX
3. Institute of Pharmacology, University Duisburg-Essen, Essen, Germany

Introduction: Atrial fibrillation (AF), the most common cardiac arrhythmia, is projected to affect 15 million Americans by 2030. Enhanced activity of the NLR family pyrin domain containing 3 (NLRP3) inflammasome has been linked to AF pathogenesis. Gasdermin D (GSDMD), a downstream effector of inflammasome activation, is cleaved into N-terminal (GDnt) and C-terminal fragments. In immune cells, GDnt facilitates the release of proinflammatory cytokines, such as IL-1β, and induces pyroptosis via pore formation. However, the function of GDnt in non-immune cells, such as cardiomyocytes (CMs), remains unclear.

Methods and Results: To elucidate the role of GDnt in CMs and its contribution to AF pathogenesis, we overexpressed GDnt specifically in atrial CMs using adeno-associated virus (AAV) delivery in C57Bl6/J mice (hereafter referred to as aGDnt mice). C57Bl6/J mice that received the AAV-expressing Flag protein were used as controls. Four weeks post-viral injection, atrial-specific overexpression of GDnt in aGDnt mice was confirmed via western blotting. Programmed intracardiac stimulation studies revealed that aGDnt mice exhibited increased AF inducibility. While GDnt is a known pyroptosis effector, atrial CMs of aGDnt mice lacked signs of pyroptosis. Despite increased propidium iodide uptake in aCMs, lactate dehydrogenase release - a hallmark of cell lysis - remained unchanged, suggesting incomplete pyroptosis. Interestingly, western blotting and immunohistochemistry analyses revealed increased expression and sarcolemmal localization of the endosomal sorting complexes required for transport (ESCRT) complex, a membrane repair machinery, suggesting a potential protective mechanism that repairs GDnt pores at the CM membrane. To assess whether GDnt pore formation was necessary for AF, we introduced a pore-forming-deficient GDnt-AAA mutant into a separate cohort of C57Bl6/J mice. These mice showed reduced AF susceptibility. Western blotting and immunostaining confirmed the enriched localization of GDnt protein at the mitochondria of aGDnt mice but not of aGDnt-AAA mice. Electron microscopy revealed mitochondrial swelling and deformation in atrial tissue of aGDnt mice, accompanied with increase mitochondrial ROS production and abnormal intracellular Ca2+ release. These changes

were absent in aGDnt-AAA mice. Finally, treatment with the mitochondrial-specific antioxidant TEMPO mitigated AF susceptibility in GDnt mice.

Conclusion: Our results demonstrate that restricted expression of GDnt in atrial CMs is sufficient to promote atrial arrhythmogenesis. The localization of GDnt-pores at mitochondria could impair mitochondrial function and homeostasis, thereby promoting arrhythmogenic Ca2+ release events.

Targeting mitochondrial stress may offer new therapeutic strategies for AF.

Restoration of Endothelial Glycocalyx and Reversal of Pro-Atherosclerotic Endothelial Dysfunction with S1P and Heparan Sulfate Derivative Co-Therapy

Kaleigh Pentland, Northeastern University
NHLBI
Poster 11
kpentland2000@verizon.net

Introduction: Atherosclerosis and consequent cardiovascular diseases remain the leading cause of death, worldwide. Thus, it is critical that we identify new therapeutic targets and develop novel treatments for these disorders. Deformation of arterial blood vessels and atherosclerotic plaque aggregation result from disturbed blood flow, which impairs the endothelial cells lining the blood vessel walls. This impairment includes structural and function damage to the glycocalyx (GCX), a protective sugar mesh coating the surface of endothelial cells. This results in increased inflammation and vascular permeability, decreased vascular tone, reduced nitric oxide synthase production, and dysregulated biochemical signaling, all of which contribute to the progression of atherosclerosis. Due to its role in preventing atherosclerosis, the GCX is a prime target for cardiovascular treatments.

Objective: This study evaluated the therapeutic properties of our albumin-bound sphingosine-1-phosphate (S1P) and heparan sulfate (HS) derivative co-treatment on damaged endothelial cell glycocalyx structure and function. We hypothesized that the co-treatment would repair structural GCX and restore GCX mechanotransduction function in disturbed flow (DF) regions. S1P is a bioactive lipid mediator that preserves the GCX and reduces vascular permeability, while albumin boosts S1P stability and bioactivity. An HS derivative, heparin sodium, was used in our co-treatment. Heparin sodium is commercially available, already used in clinics as an anticoagulant, and is cheaper than heparan sulfate. By using this derivative, this project also aimed to make the co-treatment a more affordable and more accessible option for treating cardiovascular disease.

Methods: Two DF models were utilized in this study: a partial carotid ligation mouse model for in vivo and a parallel-plate flow chamber containing Human Coronary Artery Endothelial Cell (HCAEC) cultures for in vitro. The partial ligation surgery induced acute DF in the left carotid artery, while the un-ligated right carotid artery acted as a uniform flow (UF) control in each mouse. The step-studded topography of the parallel plate flow chamber replicated DF regions upstream and UF regions downstream of the cell cultures, allowing experimental and control regions to experience flow simultaneously. The co-treatment was delivered to both models: the mice received a single injection five days post-surgery, and the flow chamber was exposed to media containing the co-treatment for the duration of a 12-hour flow. Fluorescent staining, assessment of cellular alignment, ultrasound and confocal imaging, and relevant statistical analyses were utilized to determine the co-treatment's effects on restoring GCX structure and function.

Results: The co-treatment was found to repair GCX structural integrity in vivo and in vitro, as measured by increased GCX core protein expression. The co-treatment also restored barrier function in vivo, as measured by decreased macrophage uptake into the vessel walls. Finally, the co-treatment restored vascular tone in vitro, as measured by activated eNOS (p-eNOS) expression, and vascular remodeling in vivo, as measured by reductions in vessel wall thickness.

Conclusion: The co-treatment successfully repaired GCX structure and function in DF regions and thus presents a promising new avenue for preventing cardiovascular diseases.

TSLP, IL-4 and IL-13 Increase Transcriptional Programs Associated with Hypercontractility in Human Airway Smooth Muscle

Anushka Ruwanpathirana, The Ohio State University
NHLBI
Poster 12
anushka.ruwanpathirana@nationwidechildrens.org

Authors: Anushka Ruwanpathirana, MBBS1,2, Joshua Walum, BS1, Kathryn Heyob, BS1, Rodney D. Britt Jr, PhD1,3

Affiliations:
1. Center for Perinatal Research, Abigail Wexner Research Institute, Nationwide Children's Hospital, Columbus, OH
2. Biomedical Sciences Graduate Program, College of Medicine, The Ohio State University, Columbus, OH
3. Department of Pediatrics, The Ohio State University, Columbus, OH

Rationale: Asthma involves type 2 inflammation, which promotes airway smooth muscle (ASM) hypercontractility. Type 2 effector cytokines IL-4, IL-13 and TSLP, are increased in sputum samples from individuals with asthma, and monoclonal antibodies targeting IL-4, IL-13 and TSLP pathways alleviate type 2 high moderate-severe asthma. However, the transcriptional mechanisms by which IL-4, IL-13, and TSLP promote ASM hypercontractility, particularly in the context of severe asthma, remain poorly understood. Our study examined transcriptomics and biological pathways in human ASM treated with IL-4, IL-13, and TSLP.

Methods: Human ASM cells (n=4) were isolated from lung tissue from individuals with asthma. Cells were serum starved for 48h and then treated with media only, 10 ng/mL IL-4, 50 ng/mL IL-13, or 20 ng/mL TSLP for 2h. Cells were harvested for RNA isolation. We performed RNA cleanup, purification, and library preparation for sequencing on the Illumina NovaSeq 6000. Data files were processed for de-multiplexing, FASTQC, alignment, count normalization, differential expression analysis (DEA) using R studio. DEA was defined by log2 fold change=|1.5| and adjusted p-value 0.05. Pathway enrichment analysis was performed using the gProlifer and Qiagen Ingenuity Pathway Analysis (IPA) tools.

Results: Differential expression analysis showed that IL-4 significantly changed 347 genes (164 increased, 183 decreased), IL-13 significantly changed 967 genes (600 increased, 368 decreased), and TSLP significantly changed 892 genes (593 increased, 199 decreased). Pathway analysis using gProfiler showed enrichment for Gene Ontology and Kyoto Encyclopedia of Genes and Genomes (GO/KEGG) terms, including calcium ion transmembrane transporter activity, G protein-coupled receptor (GPCR) activity, calcium channel regulatory activity and excitatory extracellular ligand- and voltage- gated monoatomic ion channel activity common to IL-4, IL-13 and TSLP cytokine treatments. Further, we found 73 differentially expressed genes

that were common to all 3 treatments, which included key pathways in ASM hypercontractility, Ca2+ regulation (ANO1, KCNH1) and Rho GTPase signaling (ARHGEF35, RAPGEF4, ARHGAP4). Upstream analysis using IPA showed master regulators SIX1 and IKBKG, which regulate GPCR signaling and NF-kB, and STAT6, which regulates PI3K related signaling, as potential drivers of the contractility regulatory network.

Conclusions: Our data suggest that type 2 cytokines IL-4, IL-13 and TSLP change gene expression in ASM. We found many genes common to their individual effects, particularly those known to promote ASM hypercontractility. These studies can lead to better understanding of the molecular mechanisms by which type 2 cytokines promote ASM hypercontractility in severe asthma. This discovery could also help identify additional strategies to therapeutically target ASM and alleviate bronchoconstriction in asthma.

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Concordance Between Virtual and Clinical Anthropometric Measures of Children and Adults: A Validity Sub-study

Jasmin Sanchez, University of Colorado School of Medicine ACCORDS
NHLBI
Poster 13
jasmin.2.sanchez@cuanschutz.edu

Objectively measured biometric data on study participants is expensive for large, population-based studies and burdensome for participants because they require in-person visits. Although remote data collection comes with many benefits (e.g., cost-effective for researchers and participants, more accessible to diverse populations, eliminates transportation and mobility issues, etc.), it has not been commonly used to measure height (HT), weight (WT) and neck circumference (NC). Sanchez et al., (2024) reviewed the studies used in the last ten years and suggested best practices that should be used for virtual measurements based on prior research. The current study takes the learnings from our previous literature review and examines how effective the above-mentioned recommendations are when implemented in a cohort study. We examine the concordance between the virtual and clinical measurements of Child and Adult HT WT, and NC.

Cholesterol Modulation of BK Currents and Cerebral Artery Diameter via Channel-forming slo1 Subunits

Elizabeth Schneider, University of Tennessee Health Science Center
NHLBI
Poster 14
eschnei7@uthsc.edu

Calcium- and voltage-gated potassium channels of big conductance (BK) play a key role in major body functions, including regulation of artery diameter. Cholesterol (CLR), an essential lipid in animal cell membranes, decreases the open probability (Po) of homotetramers of BK-forming (slo1) subunits. Moreover, cumulative Y-to-F substitutions in CLR recognition amino acid consensus (CRAC) motifs within the slo1 cytosolic tail domain (CRACs 4-10) increasingly blunt CLR action (Singh et al., 2012). However, the specific contribution of each CRAC to CLR inhibition of slo1 remains unknown. Y-to-F single substitutions in CRACs 4-10 were thus performed, and the resulting purified slo1 proteins were reconstituted into planar lipid bilayers. The voltage required to reach half-maximal Po was determined for each Y-to-F slo1 construct. Channels with Y-to-F substitution in CRAC 5, 6 or 7 were inhibited by 33 mol% CLR, as found for wild-type (WT) slo1, suggesting that these CRACs do not sense CLR. In contrast, channels with Y-to-F in CRACs 4, 8, 9 or 10 were insensitive to CLR, suggesting these CRACs sense CLR. Nanoscale differential scanning fluorimetry, however, showed protein misfolding caused by the Y-to-F substitution in CRACs 8, 9 and 10, whereas the equivalent substitution in CRAC4 (Y450F) did not. Equilibrium dialysis was performed on WT and Y450F slo1 over a range of 0-5.8 mM CLR and showed that CLR bound slo1 proteins with KD=1.1 mM. Moreover, this binding was lost in slo1 Y450F. Driven by this result and the importance of CLR and BK in regulating cerebral artery diameter, myogenic tone experiments were performed on Y450F knock-in (K/I) mice. Middle cerebral arteries were dissected, cannulated onto vessel chambers, and observed for myogenic tone development, upon which vessel diameter response to change in CLR levels was determined. De-endothelialized arteries from WT males significantly decreased diameter in response to CLR enrichment when compared to data upon CLR depletion. Supporting the role of slo1 Y450 in CLR-sensing, arteries from male Y450F K/I mice were insensitive to CLR enrichment. Lastly, arteries from WT females were insensitive to CLR, suggesting a sexual dimorphism in CLR-sensing by BK which involves a mechanism(s) other than recognition by Y450. We prove an essential role for slo1 CRAC4 in CLR binding and eventual channel inhibition, as well as the consequence of this interaction on middle cerebral artery diameter.

Cardiac Fibroblast-MHCII Contribution to Cardiac Pathophysiology in Doxorubicin-Induced Cardiomyopathy

Maria Antonia Zambrano, Tufts University
NHLBI
Poster 15
maria.zambrano@tufts.edu

Cancer patients receiving Doxorubicin (Dox), one of the most widely used chemotherapy agents, often develop cardiomyopathy and heart failure (HF), the pathological hallmarks of which include cardiac fibrosis, atrophy, contractile dysfunction, and increased levels of circulating pro-inflammatory cytokines. However, the immune mechanisms involved are largely unexplored. Cardiac fibrosis and cardiac inflammation co-exist in several etiologies of HF, with cardiac fibroblasts (CFBs) adopting "immune-like" functions such as chemokine production and expression of major histocompatibility complex II (MHCII), required for antigen presentation. We hypothesized that Dox induces a pro-inflammatory CFB state, characterized by MHCII expression and contributing to cardiomyopathy. We treated wild-type (WT), T cell-deficient (Tcrα-/-), and tamoxifen or vehicle Tcf21iCre/+MhcIIfl/fl mice (CFB-MhcII-/- and CFB-MhcII+/+, respectively) with PBS or Dox intraperitoneally (5 mg/kg/week) for 8 weeks. We performed flow cytometry on CFBs from digested hearts (CD31-/CD45-/MEFSK4+/MHCII+), whole heart gene expression by qPCR; histological analyses with wheat-germ agglutinin and picrosirius red for cardiac atrophy and fibrosis, respectively; and echocardiography to determine contractile function. In vitro experiments were performed on isolated primary CFBs treated with Dox (0.1ug/mL) and IFNγ (100U/mL) or supernatants from in vitro generated IFNγ-producing T cytotoxic T cells (Tc1). Protein expression was analyzed by flow cytometry and immunofluorescence. Three-day in vitro treatment of CFBs with Dox resulted in the induction of Cxcl9, contributing to Tc1 migration in transwell assays, yet it was not sufficient to induce CFB-MHCII protein or gene expression, in contrast to IFN-γ or Tc1 cell supernatant-treated CFBs. Dox and IFNy synergistically induced CFB Cxcl9, but not Mhcii expression. In vivo, 8 weeks of Dox induced the expression of MHCII in a subset of CFBs in WT and not in Tcrα-/- mice. Lastly, CFB-MhcII-/- mice developed less cardiac atrophy and fibrosis, and showed improved systolic function in response to Dox, compared to CFB-MhcII+/+ littermate controls. We demonstrate that Dox induces a pro-inflammatory CFB state characterized by MHCII expression that is dependent on T cells and contributes to cardiac fibrosis, atrophy, and systolic dysfunction. Mechanistically, Dox and IFNγ work synergistically to induce CFB-Cxcl9 release and induce Tc1 cell migration that further contributes to MHC-II expression.

Enhancing Health Equity Through Culturally and Linguistically Tailored Genetics Education Materials

Grace Leon-Lozano, University of North Carolina at Chapel Hill
NHGRI
Poster 16
gleon@email.unc.edu

Unequal representation in genetic and genomic research among racially minoritized populations is primarily due to historically inequitable and unjust institutional research practices, potential mistrust of biomedical research, and a lack of access to or awareness of research opportunities. Research shows that multilingual and culturally responsive educational resources that improve health literacy can improve research participation of historically underrepresented groups. Nearly one-fifth of the U.S. population identifies as Hispanic/Latino/a/x, encompassing U.S. residents, naturalized citizens from various countries, and citizens with immigrant parents. This includes fluent English speakers and Spanish-only speakers from diverse cultural backgrounds. The growth of this population underscores a growing need for Spanish health services and resources. Given that Spanish is the second most common language spoken in the U.S., culturally appropriate Spanish-language materials are crucial for advancing equity.

To address this need, the Age-Based Genomic Screening (ABGS) study formed an academic-community partnership and co-developed educational modules to build genetic literacy and support informed decision-making. We used the Designing for Dissemination and Sustainability model from dissemination and implementation science to ensure focus on contextual fit, health equity, and eventual sustainment of the modules. The ABGS Spanish translation team includes bilingual members from diverse cultural and professional backgrounds, enabling us to create socioculturally relevant project materials. Through a robust, interactive, and transparent review process, each member provides feedback, allowing iterative modifications to ensure the final resources are both linguistically accurate and culturally appropriate for the intended audience.

An explanatory mixed-methods pilot study is underway to examine the impact of bilingual educational content and delivery methods on community engagement event attendees via surveys and semi-structured interviews. Survey questions evaluate the quality of the module translations and assess pre- and post-genomic knowledge and receptiveness to genomic research participation. The translation and cultural adaptation of the genetics education modules are critical steps towards precision public health. By making genetic information accessible to non-English-speaking populations, we aim to enhance equity in public health efforts and help empower individuals to make informed healthcare decisions.

Heterogeneity of Preferences for and Outcomes of Pediatric Genomic Sequencing by Race and Ethnicity

Taylor Montgomery, Harvard Pilgrim Health Care Institute
NHGRI
Poster 17
taylor_montgomery@hphci.harvard.edu

Introduction: Genetic conditions can substantially affect the quality of life and well–being of pediatric patients and their families. Genomic sequencing (GS) is rapidly being integrated into pediatric clinical care. At the same time, there is increasing attention being paid to the lack of diversity in genomics research and issues of access and equity related to GS in clinical settings. The overall goal of this research is to understand whether and how preferences for, and outcomes of, clinical GS for newborn and pediatric patients differ by race and ethnicity.

Methods: We updated a literature review of stated preference methods for genetic testing by Ozdemir and colleagues (2022). We screened the original Ozdemir articles and new articles, identified through seven databases for racial and ethnicity population reporting and preference heterogeneity by race and ethnicity. In addition, we conducted an analysis of 2011-2023 patient record data from the Boston Children's Hospital Neonatal Intensive Care Unit (NICU). Our research aimed to analyze order rates, completion rates, and diagnoses by race and ethnicity for microarray, exome and genome sequencing, and gene panels.

Results: Our updated literature review, building upon the Ozdemir study, found that 18 articles examining preferences for genetic testing reported race and ethnicity. Of those 18, eight reported preference heterogeneity by race and ethnicity. Two articles reported preference heterogeneity by race and ethnicity. Within the clinical NICU setting, white infants were 1.64x more likely to receive a microarray order than Black infants, and Arab infants were 3.34x more likely to receive a microarray order than Hispanic infants. We did not find evidence of significant disparities in outcome of testing by race and ethnicity among infants who completed an exome/genome and gene panel and those who received a completed test and diagnosis.

Conclusions: Many studies in the literature review did not have representative study populations and did not report on all major racial and ethnic groups. Many factors can impact the patient experience and clinical outcomes associated with pediatric GS, such as familial characteristics, health care access, diagnosed condition, and institutional and public policies. While race and ethnicity were not significant predictors of genetic testing outcomes, our research continues by examining the impact of the child opportunity index (COI) in the NICU on outcomes.

Antigen Persistence Following mRNA Vaccination and the Immune Consequence of Lymph Node Stromal Cell Delivery

Robert Belfon, University of Colorado Anschutz Medical Campus
NIAID
Poster 18
robert.belfon@cuanschutz.edu

Authors: Robert Belfon, Erika Lasda, Jay Hesselberth, Beth Tamburini

Affiliations: Department of Medicine: GI/Hepatology, School of Medicine, University of Colorado Anschutz Medical Campus

mRNA vaccines have demonstrated their usefulness on a global scale in recent years. They elicit potent humoral and cell mediated responses, but the specific mechanisms by which these responses are produced still require investigation. Our lab described a process termed “antigen archiving”, during which antigen is retained within lymph node stromal cell (LNSC) subsets following viral infection and subunit vaccination bolsters/prolongs memory CD8 T cell responses. Whether mRNA vaccines utilize this mechanism to promote immunity has yet to be determined. Data suggest mRNA-derived antigen persists within LNSC of C57/BL6 mice for at least 3 weeks following subcutaneous or intramuscular delivery. We investigate the immune consequence of this prolonged antigen retention using ionizable lipid nanoparticles (LNP) to deliver mRNA constructs encoding the model antigen ovalbumin, as well as a fluorescent siinfekl-GFP to monitor antigen-specific T-cell responses and localization of antigen within murine lymph nodes (LNs). We identified LNP formulations facilitating differential uptake/translation within LNSC, which also demonstrated robust antigen-specific CD8 T cell responses and persistence of antigen presentation within LNs for at least 3 weeks, in vivo. We plan to interrogate the immune consequences of enhanced stromal cell targeting and subsequent antigen retention following mRNA vaccination. A better understanding of mRNA and protein delivery and retention will inform future vaccine design.

Expanding the Syphilis Molecular Toolbox: in vitro and in vivo Characterization of Treponema Pallidum Expressing a Constitutive Green Fluorescent Protein Reporter

Kristina Delgado, University of Connecticut Health
NIAID
Poster 19
kdelgado@uchc.edu

Authors: Kristina Delgado1, Crystal F. Vicente2, Christopher M. Hennelley3, Farhang Aghakhanian3, Jonathan Parr3, Kevin Claffey4, Justin D. Radolf1, 5-8, Kelly L. Hawley1,2,6,8, and Melissa J. Caimano1,2,5,8

Affiliations: Departments of 1Medicine, 2Pediatrics, 4Cell Biology, and 5Molecular Biology and Biophysics, 6Immunology and 7Genetic and Developmental Biology, University of Connecticut Health, Farmington, CT, USA 3Institute for Global Health and Infectious Diseases, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA 8Connecticut Children's Research Institute, Connecticut Children's, Hartford, Connecticut, USA

Syphilis, a multistage sexually transmitted infection caused by Treponema pallidum subsp. pallidum (TPA), is known for its invasive nature and ability to evade the immune system, leading to persistent infections across various organ systems. Congenital syphilis, where TPA crosses the fetal-placental barrier, often resulting in severe fetal outcomes, exemplifies the syphilis spirochete's invasiveness. Despite ongoing efforts, syphilis cases continue to rise, with over 200,000 cases reported in 2022, including a significant increase in congenital syphilis cases. The inability to continuously cultivate TPA in vitro has been a major barrier to genetic studies aimed at identifying virulence factors and understanding host-pathogen interactions. However, the development of a refined coculture system using rabbit epithelial cells by Edmondson et al., in 2018 enabled the reproducible, long-term replication of TPA in semi-defined medium. This advancement led to the first reported genetic manipulation of TPA, opening the door for the generation of fluorescent reporters for pathogen tracking.

In this study, we genetically engineered a TPA Nichols strain to express a green fluorescent protein (GFP+ TPA). Characterization of GFP+ TPA revealed that it grows identically to the wild-type parent in vitro and retains full infectivity in rabbits. This new resource enhances our ability to visualize host-pathogen interactions in vitro and in vivo. Additionally, GFP+ TPA was utilized to assess the 'functionality activity' of antibodies in opsonophagocytosis assays using mouse bone marrow-derived macrophages and in the newly developed flow cytometry assay. These assays evaluated the impact of antibodies on GFP+ TPA growth and membrane integrity, confirming the utility of GFP+ TPA for studying immune clearance and protective immunity. This novel tool also paves the way for innovative approaches to identify TPA virulence factors essential for adherence, dissemination, and persistence within host tissues, advancing our

understanding of syphilis pathogenesis and informing the development of new therapeutic strategies.

Human DeISGylation Activity Discovered Within OTUs from Newly Tamdy Nairovirus of Human Health Concern

David Gonzalez, University of California, Riverside
NIAID
Poster 20
dgonz220@medsch.ucr.edu

Nairoviruses are a tick-borne virus genus of the arbovirus family Bunyaviridae that are emerging as dangerous human pathogens. Of the 39 negative (-) sense RNA nairoviruses known prior to 2021, several were observed to be of human consequence. With known cases of nosocomial transmission and mortality rates ranging typically from 5%-40% and 80% at the highest, Crimean-Congo hemorrhagic fever virus (CCHFV) is currently the most dangerous emerging nairovirus. However, other viruses including Issyk-kul virus, Dugbe virus, and Erve virus cause human disease of varying severity. For example, the Erve virus is linked to thunderclap headaches. With no FDA-approved vaccines or therapeutics for CCHFV or other nairoviruses, the World Health Organization (WHO) and others consider these to be dangerous emerging human pathogens. Within recent years, newly discovered viruses belonging to the Nairoviridae species Tamdy have been found in Japan and China: Yezu (YEZV), and Tacheng Tick Virus-1 (TTV1) and Songling (SGLV), respectively, and cause febrile illness in humans. In the U.S., a fourth nairoivirus, Pacific Coast Tick nairovirus (PCTN), was found in Mendocino County, California within a tick species that is known to transmit viruses to humans. An emergent body of literature has identified an evasion mechanism colocalized within the L protein, known as the viral homologue of the ovarian tumor protease (OTU) superfamily. Members of this OTU superfamily have been shown to possess deubiquitinating and species-specific deISGylating activity that can reverse post-translational modifications (PTMs) on host proteins that function as key immunological regulators, as well as potentially contributing to zoonotic drift. The overarching goal of this proposal seeks to evaluate the in vitro correlation of variations within the Tamdy nairovirus OTU structure and substrate-specificity for ubiquitin and certain species ISG15, and assess the impact of observed differences on the ability of these OTUs to engage host immunological pathways. Therefore, the central hypothesis of this proposal is that variations exist in the Tamdy nairovirus OTU structure and substrate-specificity for ubiquitin and certain species ISG15 versus CCHFV OTU result from evolutionary pressure to target specific host immunological pathways. To test this hypothesis, I will use a multidisciplinary approach to assess the structural and functional identity of these newly identified Tamdy nairovirus OTUs as described in Aims 1, 2, and 3. Collectively, these data will provide critical insight into the evolutionary trends within Tamdy nairovirus OTUs that facilitate the ongoing zoonotic drift towards human hosts. This knowledge will be key to identifying new nairovirus threats to human health.

CD155-TIGIT-CD226 Mediated Immune Modulation in Tuberculosis Pathogenesis

Louis Hopkins, Emory University
NIAID
Poster 21
lhopki3@emory.edu

Tuberculosis (TB) is a leading infectious killer with about 1.6 million people dying from the disease each year. Currently, the only vaccine available for TB, live-attenuated Bacillus Calmette-Guérin (BCG), has poor efficacy against pulmonary TB. To develop an effective vaccine for TB, we need to understand the immunosuppressive and evasion mechanisms induced by Mycobacterium tuberculosis (Mtb). We have previously shown that Mtb infects and impairs dendritic cell (DC) functions and suppresses optimal antigen-specific T cell responses. We now find that Mtb prevents expression of CD155 on DCs through the Mtb Hip1 protease. CD155 is known to modulate T cell function in cancer and autoimmune disease through its ligands, TIGIT and CD226, to promote anti-inflammatory and proinflammatory conditions, respectively. Therefore, we hypothesized that Mtb manipulates CD155 to suppress Th1/ Th17 polarization and proliferation, which are important for Mtb control, thereby promoting TB disease. Using in vitro co-culture assays and blocking antibodies, we examined the role of CD155 in DC effector functions and Th phenotype/polarization in murine cells. Further, we used high-dimensional flow cytometry to characterize human Mtb-specific memory CD4, CD8, and T-regulatory subsets and found evidence for significant heterogeneity in CD155/TIGIT/CD226 expression in individuals with asymptomatic latent TB infection. Preliminary data suggest that TIGIT expression on Mtb-specific T cells is associated with reduced proliferation, while CD226 promotes effector memory functions. Ongoing studies include transcriptomic profiling of Mtb-specific T cells from individuals with latent and active TB to investigate how TIGIT+ versus CD226+ signaling impacts protective immunity against TB.

Correlates of Intestinal Fatty Acid Binding Protein Levels, a Marker for Intestinal Injury in a Cohort of Kenyan Children Under 5 at Hospital Discharge for Non-traumatic Causes

Olivia McCollum, University of Washington
NIAID
Poster 22
oliviam3@uw.edu

Environmental enteric dysfunction is implicated in substantial morbidity, mortality, and malnutrition among young children living in low- and middle-income countries. Intestinal fatty acid binding protein (I-FABP), a plasma-based biomarker of intestinal injury, has been associated with enteric disease severity and illness recovery in populations living in high-income settings. We therefore sought to characterize I-FABP levels among Kenyan children recently hospitalized for non-traumatic causes and determine correlates of high I-FABP levels at enrollment. Plasma samples from children under 5 years enrolled in the Toto Bora trial, a randomized controlled trial testing the efficacy of post-discharge azithromycin use on mortality and re-hospitalization during the 6-month follow-up period, were tested for I-FABP concentration using enzyme-linked immunoassays (ELISA). Linear regression models with robust standard errors, adjusted for age and recruitment site, were used to identify correlates of mean I-FABP levels. Among the 1361 children with available blood plasma samples, the mean I-FABP level at discharge, prior to randomization, was 1850.9 pg/mL (SD: 1251.5 pg/mL). Children who were underweight (WAZ<-2) had mean I-FABP levels 409.9 pg/mL (95% CI: 187.9, 631.9) higher than those who were not underweight ($p<0.001$) and stunted children (HAZ<-2) had 233.3 pg/mL (95% CI: 66.3, 400.2) higher mean I-FABP levels than those who were not stunted ($p<0.006$). Each month increase in age was associated with a 10.2 pg/mL (95% CI: -14.2, -6.3, $p<0.001$) decrease in I-FABP level. Children who received antibiotics during their hospital stay had 282.5 pg/mL (95% CI: -542.9, -22.2) lower I-FABP levels when compared to children who did not ($p=0.033$). Enteric pathogen infection at enrollment with adenovirus, astrovirus, campylobacter, cryptosporidium, norovirus GI/GII, rotavirus, and Sapovirus (each with $p<0.05$) were each associated with higher I-FABP levels compared to children without any pathogen detected at enrollment. Finally, children with pit latrines as their main toilet type at home (+283.7 pg/mL, 95% CI: 116.4, 451.1) as well as children with unimproved water sources at home (+212.4 pg/mL 95% CI: 25.0, 399.8) had higher I-FABP levels than children with flush toilets ($p=0.001$) and access to clean drinking water ($p=0.026$). We did not find statistical evidence of sex assigned at birth, breastfeeding status, HIV exposure status, or caregiver income being associated with significant differences in I-FABP levels at hospital discharge. Further analyses will explore the change in I-FABP levels from enrollment to 3-months post-discharge as well as elucidate the impacts of azithromycin randomization on those changes.

CMV, Immune Activation, and Mucosal Immunity in Chronic HIV Infection

Ramatoulaye Ouattara, University of California Davis
NIAID
Poster 23
rhouattara@ucdavis.edu

Cytomegalovirus (CMV) is an opportunistic pathogen that causes pneumonia and other severe complications in immunocompromised patients, including those with human immunodeficiency virus (HIV). CMV in the context of HIV has been well studied. Greater than 95% of HIV-infected persons are co-infected with CMV, and co-infection is associated with increased inflammation and co-morbidities, including metabolic syndrome and cardiovascular disease. Our collaborators demonstrated that CMV infects intestinal epithelial cells in the gastrointestinal mucosa and disrupts tight junctions, likely contributing to microbial translocation and increased immune activation in people living with HIV. Although CMV infection elicits a large pool of CMV-specific CD8 T-cells in the blood, our preliminary data suggest that these cells are rare in the gastrointestinal mucosa. CMV-specific CD8 T cells are important for controlling CMV reactivation and protecting against CMV disease. To investigate the host response to CMV, we will access the SCOPE cohort, a large longitudinal cohort of well-characterized HIV-infected and uninfected persons of diverse demographic and clinical backgrounds based at the University of California, San Francisco. With this cohort, we will be using both blood and gut samples from HIV+/CMV+ and HIVneg/CMV+ participants. We hypothesize that the body's failure to control CMV infection in the GI tract is partly due to the inability of CMV-specific T-cells to localize to the gastrointestinal mucosa.

The NF-KB Binding Site in the Ifnb1 Promoter is Indispensable for Resistance to Pathogenic Viruses and Defines a Predominant Role of lfnb1 Over Ifna Genes

Carolina Rezende Melo da Silva, Thomas Jefferson University
NIAID
Poster 24
carolina.rezende.melo.da.silva@jefferson.edu

Type I interferon (IFN-I) signaling through the IFN-I receptor promotes the transcription of hundreds of interferon-stimulated genes (ISG) that protect from viral infections. Most mammals encode multiple IFN-I isoforms, comprised of one IFN-β and multiple IFN-αs (14 in mice, 13 in humans). It is unknown why there are so many IFN-I isoforms. The promoter of Ifnb1 (encoding IFN-β) binds the transcription factors AP-1, IRF3, and NF-κB, which are constitutive, and IRF7, which is an ISG. The promoter of Ifna4 (encoding IFN-α4) binds IRF3 and IRF7, while the promoters of all other IFN-α genes (non-α4) bind only IRF7. To test whether individual IFN-I differentially or redundantly protect against viral infections, we used the CRISPR/Cas9-based improved-Genome editing via Oviductal Nucleic Acids Delivery (iGONAD) method to inactivate one or multiple IFN-I genes in C57BL/6 (B6) mice. Ifnb1-/- and, to a greater extent, Ifna4,b1-/- (deficient in Ifnb1 and Ifna4) mice were significantly more susceptible than wild-type (WT) B6 mice to lethal infection with the Orthopoxvirus ectromelia virus, and to the highly virulent NY2000 and attenuated Kunjin strains of the flavivirus West Nile virus (WNV). On the other hand, Ifna4-/-, Ifna1,5,7-/- (deficient in three IRF7-only regulated IFN-α) and Ifna16-6-/- (deficient in six IRF7-only regulated IFN-α) mice suffered increased viral loads but were as resistant to lethal ECTV and WNV infections as B6 mice. Thus, the various IFN-I isoforms are non-redundantly protective against ECTV and WNV, but only IFN-β is uniquely critical to resist their lethality. However, in the absence of all Ifna genes, mice become highly susceptible to WNV but not to ECTV infection. Because NFκB is essential to resist ECTV infection, we also made Ifnb1delPRDII mice with a deletion of the NFκB binding site (PRDII) in the Ifnb1 promoter and found that they were more susceptible to ECTV and WNV infection than B6 mice. These data indicate that Ifnb1-NFkB axis has a predominant role for protection from ECTV infection while Ifna-IRF7 axis is essential to resist WNV infection.

Investigating the Impact of Tissue Maturity on Cartilage Homeostasis in Inflammatory and Mechanical Stress Conditions

Vianna Martinez, Duke University
NIAMS
Poster 25
vianna.martinez@duke.edu

Purpose: Osteoarthritis (OA) is an age-related disease that is exacerbated by inflammation and altered mechanical loading. Thus, the aim of this study was to directly examine if skeletal maturity impacts cartilage tissue homeostatic responses to increasing magnitudes of dynamic compression in the presence or absence of the inflammatory mediator IL-1.

Methods: Explant harvest: Knees from skeletally immature (6–8-week-old) and mature (2–3-year-old) female pigs were obtained as waste tissue (N=9/immature, N=3/mature). Cartilage tissue explants were collected from the femoral condyles using 5mm biopsy punches. Immature explants were trimmed to approximately 1.7mm, maintaining the superficial zone, to achieve a consistent size for loading. Mature explants were kept full-thickness, with an average height of 0.84mm. Mechanical loading: Explants were subjected to 0%, 10%, 20%, or 30% dynamic compression at 1 Hz for 3 hours/day for 3 days, with or without 100pg/mL IL-1α. Immediately after the last loading session, explants were snap-frozen and media was collected. Following lyophilization of explants, dry weights were taken, and explants were digested in papain. Biochemical assessments: In the media, sulfated glycosaminoglycan (sGAG) release (dimethylmethylene blue [DMMB] assay), and total matrix metalloproteinase (MMP) activity (MMP activity assay) were measured. In papain-digested explants, tissue DNA content (Picogreen assay) and sGAG content (DMMB assay) were assessed. All data was corrected for the dry weight of the samples. Statistics: Data that was not normally distributed was log2 transformed for statistical analysis (sGAG release) or cosine transformed (MMP activity). Three-way ANOVAs followed by Tukey's post-hoc test were performed to determine the effect of tissue maturity, IL-1, load, and/or the interaction of these factors. A p-value <0.05 was considered statistically significant.

Results: As expected, tissue DNA content was significantly lower in mature tissue than immature tissue ($p<0.0005$). Tissue sGAG content was significantly lower in mature tissue ($p<0.0001$) and was further reduced by IL-1 exposure ($p<0.001$). As a reflection of this lowered tissue sGAG content, mature cartilage also had higher amounts of sGAG release in the media compared to immature cartilage ($p<0.0001$). Moreover, IL-1 exacerbated sGAG release in the mature tissue ($p<0.0001$). Interestingly, there was an interactive effect of load and maturity on sGAG release, such that the mature tissue had higher load-induced sGAG release than the immature tissue ($p<0.05$). Though not significant in this pilot study, total MMP activity was trending towards an increase due to IL-1 in mature cartilage compared to immature cartilage ($p=0.299$).

Conclusions: Our findings reveal that IL-1 induces matrix degrading effects in mature cartilage, but that immature cartilage is resistant to these effects. In this study, mechanical loading promoted sGAG release in mature tissue, but no other load effects were detected. However, additional analyses with increased sample sizes are necessary to deduce further effects of load and IL-1. Our results suggest that further studies unraveling the mechanisms behind immature cartilage resilience to IL-1 may be insightful to help develop strategies to prevent or slow, age-related OA development.

Monitoring Multiple Sclerosis with IL-23 Responsive Engineered Cells

Gabriela Garza, University of Michigan
NIBIB
Poster 26
gabiga@umich.edu

Autoimmunity is a growing global concern. Multiple sclerosis (MS), specifically, is a neurodegenerative disease in which the immune system attacks the central nervous system and disrupts signal transduction, affecting over 2.5 million people worldwide. We aim to engineer cellular sensors for early detection and continuous monitoring of MS, and autoimmunity broadly, to affect earlier and more timely treatment and improve patient outcomes.

The cytokine interleukin-23 (IL-23) is involved in adaptive immune function and important in MS. Our group assembled 48 synthetic cell receptors with binding regions specific to IL-23 using Modular Extracellular Sensor Architecture (MESA). MESA is a style of receptor composed of two chains that dimerize upon binding a soluble ligand. Each receptor includes two naturally derived transmembrane domains, two different extracellular binding regions for IL-23 made of nanobodies and/or an engineered protein binder, and a transcription factor that induces expression of a fluorescent reporter upon activation. Plasmids encoding each receptor design were transiently transfected into HEK293FT cells in high-throughput and evaluated for surface trafficking and IL-23-induced activation using flow cytometry.

All receptor designs traffic to the surface significantly better than the negative control. During initial functional screening, 18 receptor designs showed inducible fluorescent signal in the presence of secreted IL-23. The greatest number of successful receptor designs combined a nanobody binding to the N-terminal domain of the p40 subunit and a nanobody capable of binding to either the p19 or p40 subunits of IL-23. The 7 receptors with the greatest inducible signal were tested under various concentrations of media-supplemented IL-23. Of these, two receptor designs showed inducible signal to exogenous ligand.

These results identify two promising receptor designs. Moving forward, we will amplify the induced signal, characterize receptor dynamics of PEG-encapsulated cell sensors, and validate our cell sensors in a mouse model of MS. These results inform future receptor engineering for IL-23 as the receptor designs with the most pronounced signal-noise ratio targeted both the p19 and p40 regions of IL-23. Moreover, we are one step closer to building a real-time monitor of autoimmunity to help patients identify and manage their diagnosis.

Characterization of Initial Immune Response by HL-60 Derived Neutrophils and Their Role in Host-pathogen Interaction

Anyelo Diaz, University of Massachusetts Lowell
NIDCR
Poster 27
anyelo_diaz@student.uml.edu

Introduction: Oral tissue homeostasis depends on finely regulated interactions between the host, microbiota, and immune cells within the periodontal sulcus. Disruption of these balanced interactions can lead to mild inflammatory conditions (i.e., gingivitis) or progress to chronic states (i.e., periodontitis). These conditions, if left untreated, can contribute to systemic diseases due to infiltration of pathogens into the bloodstream. However, understanding the ways in which these actors shape host physiology remains a challenge, considering the current setbacks in clinical and in-vitro studies (e.g., complexity, inability to control experimental variables, short lifespan). Therefore, understanding the initial mechanisms of interactions among the host, microbiota, and the immune system in healthy and disease states within the periodontal niche is crucial to identify disease onset and develop strategies to reverse gingivitis. Thus, this work focuses on the characterization of interaction mechanisms of HL-60 derived neutrophils and patient-derived microbiota (healthy and inflamed) in a 3D gingival tissue model.

Methods: HL-60 cells were induced into neutrophil-like cells via all-trans Retinoic acid and Dimethylsulfoxide, and differentiation was assessed via fibrocyte (FC) (CD11b) Giemsa staining (nuclear lobulation). To induce neutrophil's activation, healthy cells (H.K.H.) and gingivitis (H.K.G.) heat-killed microbiota were incubated for 4h at MOI10. Phorbol 12-myristate 13-acetate (PMA), opsonized zymosan (OZ), Escherichia coli lipopolysaccharide (E.C. LPS), heat-killed Porphyromonas gingivalis (H.K.P.G.), and artificial saliva (AS) were used as controls.

Findings: HL-60-derived neutrophils (dHL-60) exhibited complete differentiation (CD11b+), maturation (nuclear lobulation), and a functional oxidative burst (ROS) after PMA and OZ treatment. They also showed stronger activation when exposed to human plaque samples compared to traditional controls (E.C. LPS and H.K. P.G.). Notably, dHL-60 responded more robustly to dysbiotic plaque (H.K. GI) than to healthy plaque (H.K. HE), indicating recognition of a dysbiotic state. Future studies will assess HL-60 treated with AS and incorporate both cell types into a 3D gingival tissue model to better mimic oral homeostasis in the periodontal niche.

One Embryonic rWNT5A Treatment Results in Robinow Syndrome-like Craniofacial Phenotype

Claire Houchen, University of Missouri-Kansas City
NIDCR
Poster 28
houchenc@umkc.edu

Objective: Wnt family member 5A (WNT5A) signaling is a major player in craniofacial development, as well as in osteoblast-lineage and osteoclast differentiation and activity. Studies in humans, mice, and chicks have shown a role for the WNT5A signaling pathway in craniofacial development. For example, WNT5A mutations cause maxillary hypoplasia, frontal bossing, and upturned nose in patients with Robinow Syndrome. We sought to determine to what extent recombinant WNT4A (rWNT5A) administration during early osteogenesis results in a Robinow Syndrome-like phenotype.

Methods: To determine the effects of supraphysiological WNT5A on craniofacial development during the initiation of bone mineralization, quail (Coturnix japonica) embryos were given one dose of 0.125 mg/kg recombinant WNT5A or vehicle at stage HH33, when the jawbone is first starting to mineralize. Embryos were collected at stage HH39, when there is osteoclast activity and the jaw is highly mineralized, and skulls were analyzed in 2D and 3D. Data were analyzed by a two-tailed, unpaired t-test or by principal component analysis, as appropriate. Furthermore, expression of genes involved in WNT5A signaling and known to be associated with Robinow Syndrome were assessed by quantitative PCR.

Results: WNT5A, receptor tyrosine kinase-like orphan receptor 2 (ROR2), disheveled 1 (DVL1), and frizzled 2 (FZD2) expression did not greatly vary in quail lower jaw tissue between stages HH33 and HH39 ($p>0.05$, n=7/stage). Micro-computed tomography scans of the skull revealed craniofacial changes in rWNT5A-treated embryos. rWNT5A-treated embryos had a significant, 3.2% decrease in midface length ($p<0.05$, $d=-1.53$) and a trend towards decreased premaxilla length ($p=0.069$, $d=-1.01$). Generalized Procrustes analysis of the nasal ridge and the frontal bone revealed a convex nasal process of the premaxilla and frontal bossing in rWNT5A-treated embryos.

Conclusions: The skull changes in quail embryos given a single dose of rWNT5A demonstrate that WNT5A signaling plays an important role in craniofacial development at later stages of embryonic development than previously predicted, and a single dose of rWNT5A at a later developmental stage results in craniofacial changes reminiscent of craniofacial changes in patients with Robinow Syndrome. Investigation of the WNT5A pathway in specific cell types may provide a clearer picture of how this pathway influences craniofacial development.

Porphyromonas gingivalis Impacts Host Cell Metabolism and Autophagy Pathways in Human Brain Microvascular Endothelial Cells

Brianyell McDaniel Mims, Medical University of South Carolia
NIDCR
Poster 29
brianyellm@gmail.com

Porphyromonas gingivalis (P. gingivalis) is a major pathobiont implicated in chronic periodontitis and has recently been underlined as a novel reputed contributor in the progression of Alzheimer's Disease (AD). The specific mechanisms in which P. gingivalis contributes to the etiology of this disease remains to be investigated. However, there is growing evidence that brain microvascular endothelial cells (BMVECs), composers of the blood- brain-barrier (BBB), may play a role in disease formation. Therefore, we hypothesized that P. gingivalis travels to the BBB, where it successfully invades and targets major endothelial cell homeostatic metabolic and host cell degradation pathways for intracellular growth and survival in human BMVECs. Our preliminary studies show that Glutamine (Gln) and Glutamate (Glu) are beneficial to the exponential growth of P. gingivalis in vitro and are essential amino acids for proper BMVEC function. In this study, we investigated the facilitation of Gln to Glu conversion induced by P. gingivalis and found that Glutaminase-1 (GLS-1) was temporarily induced over a span of 24 hours. Likewise, we observed significant increases in Glu production in the cytoplasm as well as in the extracellular space following P. gingivalis infection for 3 hours and 6 hours. Inhibition of GLS-1 with the pharmacological inhibitor, BPTES, resulted in a gradual decline in Glu conversion and a significant decrease in the intracellular survival levels of P. gingivalis over a span of 24 hours. Lastly, we discovered that P. gingivalis simultaneously induced a pro-bacterial form of autophagy, characterized by the presence of microtubule-associated protein light-chain 3C (LC3C) autophagosomes. LC3C was deemed equally crucial in the intracellular life of the bacterium via siRNA silencing studies, and its induction/lipidation was dependent on Gln-Glu metabolism. These results signify that P. gingivalis is capable of invading BMVECs, where it scavenges host cell Gln/Glu and induces GLS-1 to successfully replicate and survive in persistent LC3C- rich autophagosomes.

Antimicrobial Peptide Hydrogel Therapeutic for Apical Periodontitis Treatment

Laura Osorno, New Jersey Institute of Technology
NIDCR
Poster 30
laura.l.osorno@njit.edu

Authors: Laura Osorno 1,2, Gelavizh Gharati 1, Ericka Delgado 1,2, Marleen Hanna 2, Abhishek Roy 1,2, Corey Heffernan 1, Carla Cugini 2, Emi Shimizu 2, Vivek A. Kumar 1

Affiliations:
1. Department of Biomedical Engineering, New Jersey Institute of Technology, Newark, NJ
2. Department of Oral Biology, Rutgers School of Dental Medicine, Newark, NJ

Introduction: Apical periodontitis (AP) is a common local inflammatory disease caused by pulp infection from oral bacteria, with about 50% of the global population having at least one tooth with AP. This may occur due to advancement of dental caries, trauma, or operative dental procedures. Apical periodontitis impacts patients in different ways, ranging from no clinical signs or symptoms to severe destruction of the underlying bone, with or without draining abscess. AP is typically treated by removing the intracanal microbes to prevent re-infection and placing a root canal filling. However, despite major technological advances, the incidence of endodontic failure remains high. In this work, we propose the use of an antimicrobial scaffold using self-assembling peptides (SAP) to keep the root canal microbe free as well as to allow for pulp regeneration. This research aims to evaluate the efficacy of the antimicrobial scaffolds by using an infected pulpectomy model using rats.

Materials and Methods: To accurately observe the efficacy of the antimicrobial scaffold, the study will use 5 rats, which will be separated into 5 groups. Each group will consist of 4 molars with 2 molars on each side of the mandible, which will be drilled to induce infection to the exposed dental pulp. The MILabs Vector^{6} and CT imaging will be used to confirm the presence of apical periodontitis and to quantify the periapical radiolucency. Once infection is confirmed, the animals will undergo treatment using our injectable hydrogels as experimental groups and a negative control (PBS). On days 7, 14, and 28, CT scans will be taken. Each periapical CT scan will be evaluated for periapical bone resorption, quantified as a function of the traced area of the periapical space and the area of the periapical alveolar bone region that represents the amount of tissue that was healed before and after treatment is measured. The rats will then be euthanized for the collection of the molars and tissue processing for histology and immunostaining.

Results and Discussion: In this study, animals underwent treatment with hydrogels and CT scans were used to track the infection volumes pre- and post-treatment. The treatment allowed for apical bone resorption, and regeneration of tissue. The results showed an improvement in the periapical bone resorption, up to 35% after 14 days of treatment on the treated molars.

Conclusion: Our self-assembly peptide hydrogels have antimicrobial as well as tissue regeneration properties that allow for tissue growth. In the field of pulp regeneration, our hydrogels hold potential for promoting dental pulp tissue repairs and regeneration by providing a supportive microenvironment for odontogenic differentiation.

APOD Regulates Neural Crest Migration and Otic Placode Specification During Craniofacial Development

Stephanie Peralta, Johns Hopkins University
NIDCR
Poster 31
speralt1@jh.edu

Craniofacial development in vertebrates requires the coordinated activity of neural crest cells (NCC) and cranial placodes, which together contribute to the craniofacial skeleton, cranial ganglia, and the paired sensory organs. Toward gaining insight into the mechanisms of early craniofacial development, we recently identified novel bone morphogenetic protein (BMP)-responsive genes during early NCC migration. One such gene encodes the lipocalin superfamily member Apolipoprotein D (APOD), a glycoprotein involved in lipid transport during inflammation and neuroprotection. We first determined the spatiotemporal expression pattern of APOD during early chick craniofacial development using Hybridization Chain Reaction Fluorescence in Situ Hybridization (HCR-FISH) and found that APOD is transiently expressed in delaminating cranial NCCs and is also expressed in the otic placode domain, the precursor to the inner ear. To determine the role of APOD in craniofacial development, we performed morpholino-mediated knockdown. By examining expression of SOX10 we found that APOD knockdown reduced both NCC migration and SOX10+ NCC counts in the midbrain compared to controls. We also observed a strong depletion of SOX10 expression in the otic placode after APOD knockdown, indicating that APOD plays a critical role in the establishment of both the migratory NC and otic placode. To determine how APOD regulates otic SOX10 expression, we performed HCR-FISH for transcription factors upstream of SOX10. These experiments show that APOD is required for the expression of SOX8, PAX2, and ETV4, suggesting mechanistic links between APOD and SOX10. Future experiments will determine direct targets of APOD during otic placode development. Together, these findings reveal that APOD is a critical regulator of both NCC migration and otic placode specification, and provide new insights into the molecular mechanisms underlying craniofacial development.

Evaluation of a Training Program for Velopharyngeal MRI

Taylor Snodgrass, East Carolina University
NIDCR
Poster 32
snodgrasst20@students.ecu.edu

Background/Purpose: Velopharyngeal (VP) magnetic resonance imaging (MRI) provides direct visualization of VP structures, including velar muscles, and this has led to substantial clinical interest. Despite interest in VP MRI by many cleft teams, few have implemented this new imaging modality. This may be due to a lack of training and detailed information to guide method adoption. The purpose of this study was to describe a training program used for implementing VP MRI, detail success rates for VP MRI collection at hospitals using this training program and identify factors that predict VP MRI success.

Methods: Eleven hospitals with cleft teams participated in a training program for implementation of VP MRI (which will be described), and subsequently began performing VP MRI. After completing the training and performing their first MRI, staff at each hospital completed semi-structured interviews to provide feedback on the training and their experience performing VP MRI. Hospitals completed the training sequentially; as feedback was received, the training program was modified so that subsequent hospitals received the updated program. Implementation was evaluated using three measures: proportion of scans completed successfully, proportion of scans completed successfully at a hospital after competence was achieved (i.e., after the hospital completed their first successful scan), and number of scans required to achieve competence.

Results: Overall scan success was 81% (43/53 scans). After competence with VP MRI was achieved, success increased to 89% (33/37 scans). Ten of the 11 hospitals achieved competence with VP MRI data: 60% (6/10) achieved competence with their first scan, 30% (3/10) with their second scan, and 10% (1/10) with their third scan. The following factors were associated with successful MRI completion: having a speech-language pathologist present for the scan ($p=0.007$*), having previous experience with VP MRI ($p=0.001$*), and having consistent MRI staff ($p=0.010$*). Factors not associated with successful MRI completion were: having a child life specialist present ($p=0.532$), video conferencing with an expert in VP MRI during data collection ($p=0.625$), and calling a hotline to discuss data collection with a VP MRI expert during the scan ($p=0.549$).

Conclusions: The training program was successful at preparing sites for VP MRI implementation. Hospital-specific variables associated with successful VP MRI scans include having a speech-language pathologist present for scans, having previous experience with VP MRI, and having consistent staff.

Amelogenin (Amelx) Ahosphorylation Affects ACP4 Expression

Brent Vasquez, University of Pittsburgh
NIDCR
Poster 33
bpv4@pitt.edu

Authors: Brent Vasquez 1,2, Ai Thu Bui 1,2, Lasya Bhogadi 1,2, Henry Margolis 1,2,3, Elia Beniash 1,2,4

Affiliations:
1. Department of Oral and Craniofacial Sciences, University of Pittsburgh School of Dental Medicine, Pittsburgh, PA
2. Center for Craniofacial Regeneration, University of Pittsburgh School of Dental Medicine, Pittsburgh, PA
3. Department of Periodontics and Preventive Dentistry, University of Pittsburgh School of Dental Medicine, Pittsburgh, PA
4. Department of Bioengineering University of Pittsburgh, Swanson School of Engineering, Pittsburgh, PA

Aelogenin (Amelx) phosphorylation is critical for the development of enamel. Amelx has a sole phosphorylation site at Serine 16 (S16). AMELXS16A KI mice lacking Amelx phosphorylation present with severely compromised enamel[1]. Moreover, recent studies conducted in our lab revealed that secretory enamel in AMELXS16A KI mice is acidified. Mutations in kinases are known to cause amelogenesis imperfecta (AI). Recent studies demonstrate that acid phosphatase 4 (ACP4) is expressed in Tomes' processes of secretory ameloblasts[2]. Mutations in ACP4 cause severe AI, and the mouse ACP4 KI model carrying the human mutation presents with hypoplastic prism-less enamel with ectopic calcifications, the phenotype very similar to AMELXS16A KI.

Using single-cell RNA sequencing (scRNA-seq) we found ACP4 to be significantly upregulated in the enamel organ of AMELXS16AKI mice and this upregulation was confirmed by RT-qPCR. Furthermore, immunohistochemistry revealed that ACP4 expression is higher in distal ends of AMELXS16AKI secretory ameloblasts compared to wild-type (WT) mice.

Our findings have led to the hypotheses that interactions of phosphorylated Amelx with ACP4 are essential for proper enamel formation and that changes in pH can affect these interactions. We have decided to establish an in vitro model to test this hypothesis. Specifically, literature reports show that an MDPC-23 dental papilla cell line expresses ACP4[3]. We have confirmed these findings using RT-qPCR, western blot, and immunohistochemistry. Based on these studies we have selected the MDPC-23 cell line for future studies of the effects of Amelx phosphorylation and pH changes on ACP4 expression and cell biology. We anticipate that these studies will provide new insights into the relationships between Amelx and ACP4.

1. Shin et al., JBC. 2020.
2. Liang et al., Sci Rep. 2022.
3. Choi et al., Cell Tissue Res. 364, 95-103. 2016.

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Does Successful Surgical Treatment of Hypernasality Aid in the Remediation of Compensatory Misarticulation Errors?

Jessica Williams, Phoenix Children's Hospital
NIDCR
Poster 34
jwilliams10@phoenixchildrens.com

Purpose: Investigate whether successful surgical management of hypernasality aids in the remediation of compensatory misarticulation errors (CMAs) among children with velopharyngeal insufficiency (VPI) and CMAs.

Method: Fourteen participants with VPI and use of CMAs from a larger study were included in this retrospective cohort study. The mean age at the time of preoperative evaluation was 8.9 years (SD = 1.1). Perceptual ratings of hypernasality, phonetic transcription, and anatomic measurements from magnetic resonance imaging (MRI) were performed by raters blinded to the participants' medical and surgical history. The mean percentage of CMAs produced on the American Sentence English Sample was calculated. The Wilcoxon signed-rank test was used to compare the change in CMA use pre- and postoperatively. During the study period, 71% (n = 10) of participants received speech therapy.

Results: Nine participants had resolved hypernasality after surgery and five had persistent hypernasality. Among those with resolved hypernasality, the mean percentage of CMAs significantly decreased from 14.6% preoperatively to 1.1% postoperatively ($p = .028$). For participants with persistent hypernasality, the mean percentage of CMAs decreased from 27.6% to 22%; this change was not significant ($p = .586$).

Conclusion: Resolution of hypernasality may aid in the remediation of CMAs, as participants have more advantageous anatomy to achieve velopharyngeal closure. The role of the non-invasive imaging modality of MRI is discussed, which could potentially help in determining the timeline for speech therapy to treat CMAs and surgical management to treat hypernasality.

Cholangiocytes' Primary Cilia Regulate DNA Damage Response and Repair

Estanislao Peixoto, Hormel Institute, University of Minnesota
NIDDK
Poster 35
epeixoto@umn.edu

Primary cilia have been implicated in various cancers, including cholangiocarcinoma (CCA), functioning as a tumor-suppressing organelle. Despite previous demonstrations of their suppressive role, the specific mechanisms through which primary cilia protect against cancer remain to be fully elucidated. Known components of carcinogenesis triggers related to failures in DNA damage response (DDR) and repair have been linked to the primary cilium and its basal body. To further our understanding of primary cilia's function in CCA, we investigated whether the loss of primary cilia affects DDR and DNA repair processes.

Using human cholangiocyte cell lines, we investigated the colocalization of DNA repair proteins at the cilia base and examined how experimental deciliation affects DNA repair pathways, leveraging RNA sequencing data for comprehensive insight. Deciliation was induced in cells via CRISPR-mediated knockout of IFT20, IFT88, and KIF3A, followed by assessment of cellular survival in response to cisplatin, methyl methanesulfonate (MMS), and irradiation challenges. Further analyses included evaluations of cell cycle dynamics and apoptosis rates. To quantify DNA damage, we employed comet assays and γH2AXquantification. Additionally, we measured the levels of key DDR proteins using Western blot analysis, providing a multi-dimensional perspective on the impact of cilia loss on cellular DNA repair mechanisms.

RAD51 was observed at the base of the cilia, whereas PARP1 and CHK1 exhibited localization within the cilia itself. In deciliated cells, we noted dysregulation in critical pathways, including DNA damage checkpoints, DNA double-strand break repair, and MGMT-mediated DNA damage reversal. Exposure to genotoxic agents resulted in reduced survival, increased S arrest, and elevated apoptosis in deciliated cells compared to their normal counterparts. Furthermore, deciliated cells subjected to genotoxic challenges displayed significantly higher DNA damage, as evidenced by enhanced γH2AX signals and comet assay findings. Additionally, key DDR proteins, including ATM, phosphorylated ATM (pATM), and p53, were downregulated in deciliated cells post-irradiation.

Our findings highlight the significant role of primary cilia in modulating DNA damage response and repair mechanisms. Given the urgent need for novel therapeutic approaches for cholangiocarcinoma, elucidating the intricate relationship between primary cilia and nuclear processes unveils a promising new avenue for therapeutic development.

Dihydroxyacetone Exposures Induce Genotoxicity and Metabolic Reprogramming in Cardiomyocytes

Hailey Levi, University of Alabama at Birmingham
NIEHS
Poster 36
hlevi001@uab.edu

Electronic cigarettes (e-cigarettes) have become increasingly popular in the last decade and evolved with various devices and e-liquid components. E-liquids are heated to create the aerosol the user inhales, and dihydroxyacetone (DHA) is produced by the oxidation of glycerol in the e-liquids. DHA is also an active ingredient in sunless tanning products. While DHA has been considered safe due to external exposures, the inhalation exposure risk from vaping and spray tanning has raised concerns about the inhalation of DHA. Exposures to DHA vary from these applications with micromolar to low millimolar doses potentially inhaled. Once inhaled and absorbed by cells, DHA is incorporated into several metabolic pathways through its conversion to DHA phosphate (DHAP). Given this metabolic incorporation, DHA exposure effects to highly energetic tissues, like the heart, occur.

We have characterized the genotoxicity and metabolic changes induced by DHA in acutely and subchronically exposed cardiomyocytes. Additionally, we have conducted pilot in vivo exposures in mice. We investigated changes in cell cycle, metabolism markers, mitochondrial function, nicotinamide adenine dinucleotide phosphate (NADPH) balance, and cardiac function. This work is the first to examine genotoxicity of DHA in cardiomyocytes and characterize physiologically-relevant exposures to understand potential long-term effects of DHA on cardiovascular health.

Circadian Disruption and EGFR Signaling: Unraveling the Effect of Environmental Chemicals on Placental Extravillous Trophoblast Cell Function

Jacob Moeller, University of Illinois at Chicago
NIEHS
Poster 37
jmoeller@uic.edu

Robustly expressed in the placenta is the epidermal growth factor receptor (EGFR), a key effector of many placenta cell functions, including proliferation and invasion. Notably, EGRF activation can stimulate cell proliferation and invasion and alter circadian clock function in non-reproductive tissues. We and others have reported that exposure to several high production volume chemicals can interfere with EGFR signaling and are associated with adverse pregnancy outcomes, such as preeclampsia. Additionally, disrupted molecular clock gene expression was reported in placentas from preeclamptic and pre-term birth pregnancies. Despite this, it remains largely unknown whether exposure to environmental chemicals known to alter EGFR signaling can induce placental dysfunction through disrupted circadian timing. Therefore, we are testing the hypothesis that exposure to environmental chemicals that interfere with molecular clock function through EGFR lead to placental cell dysfunction. Using the HTR-8/SVneo (HTR8) cell line as model for placental extravillous trophoblasts (EVT), the goals of this study are to determine if time-dependent EGFR activation 1) impacts circadian clock timing and 2) temporally alters placental cell migration, proliferation, and cell cycle; this study will also assess whether exposure to chemicals known to interfere with EGFR can disrupt any of these functions. Our initial experiments using serum synchronized HTR8 cells demonstrated that EVTs possess a functional circadian clock from the observations of rhythmic, antiphasic Per2 and Bmal1 gene expression. Additionally, time-dependent changes in Egfr gene expression were observed, with peak expression observed 16h following serum synchronization. To understand how EGFR activation alters circadian clock function in EVTs, HTR8 cells genetically modified to express a luciferase reporter fused to the Per2 promoter will be employed to measure real-time changes in circadian clock function (e.g., rhythm phase, amplitude, and period) in serum synchronized HTR8 cells following timed EGFR activation. Additionally, a cell wound assay will be used to evaluate how timed EGFR activation in serum synchronized HTR8 cells influences cell migration. Lastly, the effect of timed EGFR activation on cell cycle progression will be investigated using HTR8 cells genetically modified to express ubiquitination-based cell cycle indicators following timed-EGFR activation. Findings from these studies will establish the need for intact circadian timing for placental cell proliferation and invasion, but also contribute to our understanding about if and how environmental exposures may disrupt these processes. Supported by NIEHS/NIH (1R01ES035691-01S1 and 1R01ES035691-01S1 to AV-L).

The Association of Nursing with Length of Stay for Patients with Intellectual & Developmental Disabilities

Lynne Moronski, University of Pennsylvania
NINR
Poster 38
moronski@nursing.upenn.edu

The complexities of caring for individuals with intellectual and developmental disability (IDD) may translate into longer-than-needed hospital lengths of stay (LOS). Nurses are well positioned to influence the outcomes of IDD inpatients, but a large body of evidence suggests that nurses' capacity to provide optimal care to patients may depend on key organizational features, such as sufficient staff, supportive work environments, and sufficient number of registered nurses among the nursing staff. The purpose of this paper is to determine the association of these nursing resource factors with LOS in adults with IDD.

Describing Mexican American Women's Experience of Social Isolation and Discrimination and the Perceived Role of These Stressors on Eating Behavior, Obesity, and Health

Rosario Jaime-Lara, University of California Los Angeles
NIMHD
Poster 39
rjaime-lara@mednet.ucla.edu

Authors: Rosario Jaime-Lara1, MarySue Heilemann1, Lauren Clark1, Hiram Beltran-Sanchez 2, Allison Vaughan 3, Kimberly Martinez 1, Paloma Sanchez 1, Jennifer Labus 3, Lisa Kilpatrick 3, May Wang 2, Gilbert C. Gee 2, Arpana Church 3

Affiliations:
1. University of California Los Angeles School of Nursing, Los Angeles, CA
2. University of California Los Angeles Fielding School of Public Health, Los Angeles, CA
3. David Geffen School of Medicine at UCLA, Los Angeles, CA

Mexican origin (MO) women comprise the largest Hispanic subgroup of Latinas in the United States, and they have the fastest growing levels of obesity in this country. Obesity increases the risk for chronic diseases, such as diabetes and cardiovascular disease, which already disproportionately affect ethnic minorities, including MO women. As obesity rates among MO women increase at alarming rates, it is important, timely, and critical to better understand the factors contributing to obesity in this population. The current study examines social isolation and discrimination from participants' perspective, including how MO women characterize social isolation and discrimination and how they perceive these social stressors to affect their eating behaviors and overall health. We conducted five informational interviews and line-by-line coded each de-identified transcript and memo. A code book (i.e., focused code list) was created by comparing all codes in the six transcripts to identify the most salient codes. The six coded transcripts were reviewed by the team to confirm the 11 focus codes that will be used to code all subsequent interviews. Consensus meetings will continue to be held to refine the coding dictionary and the definition of each code. Data analysis will build from initial codes, starting with descriptive codes. Themes will be derived from identifying common threads through the data and will represent the most abstract level of analysis. Ten interviews of MO women with BMIs above 30 have been conducted, and interviews will continue until data saturation is reached. Here, we present the latest results, focused codes, and sample quotes. Focused codes include: looking for connection through food, coping with stress through eating, and understanding discrimination. Together these data will advance scientific knowledge by offering a more complete and patient-centered understanding of how social stress impacts obesity in ethnic minority women, specifically MO women. This is an important step towards developing culturally sensitive, holistic interventions to reduce social stressors that contribute to obesity, with the ultimate goal of collaborating with MO women to decrease and manage obesity in MO women and other ethnic minority women.

Beliefs about Social Mobility in Young American Children

Tara Mandalaywala, Boston University
NIMHD
Poster 40
tmanda@bu.edu

Although actual experiences of upward social mobility are historically low, many adolescents and adults express a belief in social mobility (i.e., that social status can change). Although a belief in upward mobility (i.e., that social status can improve) can be helpful for economically disadvantaged adolescents and adults, a belief in upward social mobility in adults is also associated with greater acceptance of societal inequality. While this belief might have similar benefits or consequences in children, no previous work has examined whether children are even capable of reasoning about social mobility. This is surprising, given that elementary-aged children exhibit sophisticated reasoning both about social status, as well as about the fixedness or malleability of properties and group membership. Across an economically advantaged group of 5- to 12-year-old American children (N = 151, Mage = 8.91, 63% racial majority, 25% racially marginalized; Mhousehold income = $133,064), we found evidence that children can reason about social mobility for their own families and for others. Similar to research in adults, children believe that others are more likely to experience upward than downward mobility. However, in contrast to adults' typical beliefs—but in line with economic realities—between the ages of 7 and 9, children become less likely to expect upward mobility for economically disadvantaged, versus advantaged, families. In sum, children are capable of reasoning about social mobility in nuanced ways; future work should explore the implications of these beliefs.

Natural Killer Cells in the Developing Cerebellum: Shepherds or Poachers of Neurogenesis?

Andrew Allee, University of Maryland Baltimore School of Medicine
NIMH
Poster 41
Andrew.Allee@som.umaryland.edu

Neurodevelopmental disorders (NDDs) have been firmly and repeatedly linked to early life inflammation and sex, with males 2-4 times more likely to be diagnosed with neuropsychiatric disorders such as autism spectrum disorder (ASD). Moreover, several NDDs present with measurable alterations in cerebellar architecture, a brain region now recognized for its role in cognition and social behavior. Despite the rigor of these observations, the underlying mechanisms are largely unknown and the potential contribution of peripheral immune cells little understood. Clear cellular protagonists are unclear in NDDs, but dysregulated natural killer (NK) cells are strongly implicated. Thus, we hypothesize that during the first postnatal week of life, NK cells function to kill newly divided cells within the developing cerebellum. Upon immune activation, we hypothesize that altered NK cell phenotype can lead to exacerbated killing and the manifestation of neurodevelopmental disorders. Past work from our lab established an enriched NK cell presence in the developing rat cerebellum compared to peripheral blood. Leveraging these findings, our project assesses NK cell contributions to typical neurodevelopment. We begin our interrogation by manipulating NK cell frequency in the developing brain. Measured by flow cytometry, we found that we can deplete brain-resident NK cells using an anti-NK1.1 antibody administered via intracerebroventricular injection. Following NK cell depletion, we quantified cell genesis in the cerebellum and found that there was no significant change in newly divided cells in each cellular layer measured: external granule cell layer, internal granule cell layer, and white matter. This endpoint was chosen because perturbation of cerebellar neurogenesis leads to impaired cerebellar function, a key characteristic of several NDDs. This study lays the foundation for understanding how NK cells may contribute or hinder typical neurodevelopment in the cerebellum while also elucidating the ongoing crosstalk between the innate immune and central nervous systems.

The Effects of Reactivation During Sleep on the Neural Representations of Episodic Memories

Sarvia Aquino Argueta, University of California, Irvine
NIMH
Poster 42
ssaquino@uci.edu

Sleep involves the reactivation of recently acquired memories, thereby shaping the neural representations supporting them. An essential feature of episodic memory is the link between a specific memory item (e.g., a chocolate cake) and the context in which it is embedded (e.g., your tenth birthday party). However, the possible role of sleep in binding memories to their contexts remains poorly understood. To investigate how reactivation during sleep impacts this binding process, we instructed participants to form stories, each linking together four objects (e.g., a gong) in unique contexts (e.g., a hike in the woods). As a measure of object-context binding, we used functional MRI to measure the overlap between neural representations for objects linked together by a story. Then, during non-REM sleep, we unobtrusively presented object-congruent sounds to selectively reactivate a subset of the object memories, a technique termed targeted memory reactivation. Sleep was followed by an additional functional MRI scan, identical to the previous one. We hypothesized that reactivating memories during sleep would either selectively strengthen object-context binding for the targeted objects, or, alternatively, keep the items segregated, prioritizing specificity. We found that targeted reactivation during sleep promoted specificity in items' neural representation in areas within the Posterior-Medial Network, as reflected by a decrease in neural overlap for reactivated vs. non-reactivated memories. The effect of selective reactivation counteracted a general increase in within-context similarity that we observed across pre- and post-nap functional MRI sessions. These results suggest that reactivation during sleep decontextualizes memories rather than strengthening item-context binding.

Resilience and Fatherhood: Exploring Self-Efficacy, Parenting Style, and Mental Health in Post-Conflict Sierra Leone

Abdulai Jawo Bah, Boston College
NIMH
Poster 43
bahabd@bc.edu

Parents who have experienced civil war are at increased risk for anxiety and post-traumatic stress disorder (PTSD), among other conditions, leading to emotional dysregulation and potentially harsh parenting practices that perpetuate a cycle of trauma for their children. Despite the critical role fathers play in child development, there is limited research on supporting fathers in conflict-affected settings, with most studies and interventions focusing primarily on mothers and their interactions with children. Sierra Leone is marked by a history of conflict, including the Ebola and COVID-19 epidemics and economic challenges. In this complex landscape, fathers face unique challenges as they navigate their roles amidst societal expectations and gender norms. Understanding the resilience of fathers in this context is crucial for fostering family well-being and community recovery. This qualitative study of a sub-sample of fathers from an ongoing longitudinal and intergenerational study of the impact of armed conflict on children explores the intricate relationship between socioeconomic status, self-efficacy, mental health, and parenting among fathers in post-conflict Sierra Leone. The Longitudinal Study of War Affected Youth, the first of its kind in sub-Saharan Africa, began in 2002, following the 11-year civil war in Sierra Leone (1991-2001). In this 22-year study, currently in its 5th follow-up wave, we conducted 30 key informant interviews with mothers (n=17) and fathers (n=13) and held 15 focus group discussions (n=57 fathers and n=68 mothers) among our longitudinal sample of war-affected youth who are now parents. We used the thematic analysis (Smith, 1992) and grounded theory (Boyatzis, 1998) approaches to data analysis, guided by the research questions and the Boyatzis approach to codebook development. Several salient themes emerged from the data, shedding light on the complex interplay between socioeconomic challenges, self-efficacy, mental health outcomes, and parenting practices among fathers in Sierra Lione. Participants expressed the struggle to provide for their families amidst environments with limited resources, which impacted their sense of self-efficacy and psychological well-being. The interviews captured pervasive concerns about economic instability and its effects on fatherhood. This study provides valuable insights into the nuanced dynamics of fatherhood in the context of low socioeconomic status and post-conflict challenges in Sierra Leone. By exploring the relationships between self-efficacy, mental health, and parenting practices, this research offers a foundation for future interventions and policies to engage and empower fathers and promote positive family outcomes in similar settings.

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iSEE: A Study of the Effects of Structural Inequities and Syndemics on Willingness to Participate in HIV Research among Black Women

Danielle Campbell, University of California, San Diego
NIMH
Poster 44
dacampbe@health.ucsd.edu

Black women (BW), while disproportionately affected by HIV globally, have been historically and drastically underrepresented in HIV research. BW face co-occurring sociostructural inequities and syndemic substance use, intimate partner violence (IPV), and adverse mental health (MH), which act as barriers to health-seeking behaviors and contribute to poor engagement in HIV prevention care and treatment. Limited research has described biological, social and structural factors that restrict women's participation in HIV research. Even less is known about how these factors affect BW participation in research, highlighting ethical concerns for efforts to conduct diverse and equitable research. The proposed theory-informed dissertation study will utilize a case-control approach among BW (n=350) where cases (n=175; those who have participated in research) and controls (n=175; those not yet participated in HIV research) will be matched based on HIV serostatus and recruitment source to elucidate the effects of sociostructural inequities, past-year substance use, past-year IPV, and adverse MH on lifetime participation in HIV research among BW in the U.S. We hypothesize that higher levels of experiences with sociostructural inequities, past-year substance use, past-year IPV, and adverse MH are associated with lower odds of lifetime participation in HIV research among cases versus controls. Participants for this dissertation study will be leveraged from existing HIV research studies and clinical and non-research efforts. To date, 32 of 350 BW have been enrolled in this dissertation study. This study will inform multilevel efforts to conduct equitable and diverse HIV research by elucidating factors that affect participation of BW in HIV research and identify solutions to increase BW participation in HIV research.

Exploring Acceptability & Potential Reach of Game-Based & Social Network Strategies for Improving PrEP & HIV Self-Testing Uptake among Latinx Men who have Sex with Men Living in an EHE Priority Jurisdiction

Lacey Craker, University of Miami
NIMH
Poster 45
lxc1301@miami.edu

Significance: The goal of this NIMH F31-Diversity fellowship is to examine the online gaming and offline friendship networks of Latinx men who have sex with men (LMSM), and the extent to which the structures and characteristics of such networks can influence LMSM access to pre-exposure prophylaxis (PrEP) information and the distribution of human immunodeficiency virus (HIV) self-testing (HIVST) kits. LMSM in Miami-Dade County, Florida, (MDC), face extreme vulnerability to HIV, given that MDC is the metropolitan statistical area with the highest HIV incidence (42.4 per 100,000) and second highest HIV prevalence (979.9 per 100,000) rates in the nation. Among incident HIV cases in MDC, 64.4% are attributed to Latinx individuals, and 81.5% are attributed to MSM. Online game-based interventions are acceptable among sexual and gender minority adolescents and adults, and have demonstrated positive effects on increasing knowledge and improving attitudes and behaviors related to HIV prevention. Few studies have investigated the combined use of online game-based and offline friendship network approaches to increase awareness and uptake of PrEP/HIVST in the LMSM community.

Approach: Guided by the Network Flow Model and Social Contagion Theory, this mixed-methods social network study will analyze and integrate two data sources collected under an R01 entitled “PrEParados: A Multi-Level Social Network Model to Increase PrEP Enrollment by Latino MSM Self-Identified as Gay, Bisexual or Straight in Miami" (PI: Kanamori, M.) from February 2022 to August 2023 (R01MH12572). First data source: egocentric and two-mode network data (N=73 egos and 153 alters). Second data source: qualitative data including 90-minute semi-structured individual interviews with LMSM online gamers (N=40). The following are the research aims: Aim 1: Characterize social networks of LMSM online gamers. This will include the description of network size, type of games played, frequency of gameplay with others, format of gameplay, and the sociodemographic characteristics of their online gaming partners. Aim 2: Understand the potential reach of LMSM online gamers to promote PrEP messaging and disseminate HIVST kits in their offline friendship networks. Egocentric and two-mode network analyses will be used to: (A) determine the structures of offline friendship and affiliation networks of LMSM online gamers, and (B) identify specific characteristics of these structures (e.g., type of games played, homogeneity, homophily) associated with the dissemination of PrEP information and distribution of HIVST kits. Aim 3: Explore the acceptability of a combined online game and offline friendship networks-based approach to promote PrEP information and HIVST kit dissemination. Qualitative findings will inform the

design of an intervention that bundles social network and online game-based approaches to increase PrEP/HIVST awareness and uptake.

Implications: This F31 study will inform the development and implementation of culturally-tailored game- and social network-based interventions to enhance HIV prevention services for LMSM and a future K99/R00 award development.

Preliminary Data — Family Dynamics and User Engagement in Co-Designing a Mental Health App: A Content Analysis of Satisfaction and Technical Challenges Using ChatGPT

Jacqueline Duong, University of Texas at Austin
NIMH
Poster 46
jduong@utexas.edu

Co-design, or participatory design, involves active collaboration among stakeholders—such as users, developers, and designers—in the design process, to ensure that the final product meets users' needs. This mixed-methods study employs content analysis to examine the extent of user involvement in co-designing a mental health application (app). By quantifying the frequency and distribution of key concepts related to user engagement, satisfaction, and feedback, the study integrates these findings with quantitative measures of user engagement and satisfaction. Twenty-four participants from a broader study on family dynamics using the Colliga app provide insights into how the co-design process influences the personalization and effectiveness of digital mental health tools.

The Coordination of Voltage-Gated Sodium Channels via Ankyrin Protein Interactions

Carina Elvira, University of Michigan, Ann Arbor
NIMH
Poster 47
celvira@umich.edu

Voltage-gated sodium channels (NaVs) are key regulators of neuronal excitability, making the dysfunction of NaVs a serious public health concern. Genetic variants in SCN2A and SCN8A, which encode the neuronal sodium channels NaV1.2 and NaV1.6, respectively, have been identified in several human patient cohorts of neurodevelopmental disorders, such as autism spectrum disorder (ASD) and developmental and epileptic encephalopathy (DEE). The proper localization of NaVs is dependent on their interactions with ankyrins, a family of intracellular scaffolding proteins that link membrane-bound proteins to the underlying cytoskeleton. Ankyrin-G, encoded by ANK3, has been established as the master organizer of the axon initial segment (AIS), a key site of neuronal excitability. Here, ankyrin-G scaffolds proteins including NaV1.2 and NaV1.6. Our lab recently identified a critical interaction between NaV1.2 and ankyrin-B, encoded by ANK2, in mature neocortical pyramidal cell dendrites, where NaV1.2 regulates dendritic excitability. Importantly, the key residues required for the binding of ankyrins and NaVs are highly conserved among ankyrins and NaVs. The objective of this study is to investigate the molecular interactions between ankyrins and NaVs, as well as the effects of SCN2A and SCN8A human disease variants within the ankyrin/NaV binding interface on channel localization and function using molecular, biochemical, electrophysiological, and imaging techniques. Our preliminary data indicate that NaV1.6 fails to localize to the dendrites to the extent of NaV1.2, suggesting that, like ankyrin-B and ankyrin-G, NaV1.2 and NaV1.6 have distinct localization patterns within neurons despite their highly conserved sequences. Our preliminary data also indicate that mutations near the ankyrin/NaV binding interface affect the binding affinity between ankyrin-B and NaV1.2. Together, these findings suggest that the regions outside of the required residues may play a role in the differential interactions between ankyrins and NaVs. These and future results will provide critical information regarding the different interactions between ankyrins and NaVs and ultimately contribute to the study of how dysfunction of ankyrins and NaVs contribute to the etiology underlying neurodevelopmental disorders.

Neurobiology of Stress-induced Social Reward Deficits

Rachel Fisher, Icahn School of Medicine at Mount Sinai
NIMH
Poster 48
rachel.fisher@icahn.mssm.edu

Diminished social interaction is a hallmark behavior in numerous psychiatric diseases, including major depressive disorder, and has been linked to increased suicide rates in recent years. However, the neurobiological mechanisms underlying altered prosocial behavior remain poorly understood. Utilizing a preclinical model of social trauma in mice, the chronic social defeat stress (CSDS) model, we aim to elucidate the brain-wide neurobiological mechanisms contributing to social deficits. To explore social investigation and social avoidance, we use a resident intruder (RI) task. The RI task involves measuring the social behaviors of our experimental mice by introducing a novel juvenile social partner to their homecage. To explore social reward and motivation, we use a social self-administration (SSA) task. The SSA task involves fixed ratio active lever-pressing to gain access to a novel juvenile mouse behind a mesh barrier. We also use the SSA task to investigate social reward deficits with a progressive ratio design, where there is a gradual increase in the number of correct responses needed to receive a social reinforcement. We identified alterations in brain reward circuitry following CSDS, highlighting the anterior cingulate cortex (ACC) as a central node involved in social interaction during the RI task through whole-brain clearing and imaging. Our data also indicated reduced SSA performances in CSDS-exposed mice, suggesting broader deficits beyond classical social avoidance. This research provides new insights into the neurobiological basis of social anhedonia, a critical symptom across various stress-induced psychiatric disorders.

Ketamine Reverses Chronic Stress-induced Mental Disorders via the Expression of Ca2+-permeable AMPA Receptors in Mice

Joshua Flowers, Colorado State University
NIMH
Poster 49
coolmanf@colostate.edu

Both preclinical and clinical studies demonstrate that chronic stress reduces AMPA receptor (AMPAR) subunit GluA1 levels in hippocampal synapses, but there are conflicting results describing alterations in hippocampal GluA2 levels under chronic stress. These results suggest that the stress-induced decrease in hippocampal GluA1 levels is correlated with both weakened excitatory synaptic transmission and altered hippocampus-dependent behaviors in chronic stress. Importantly, we have revealed that low-dose ketamine rapidly induces the expression of GluA1-containing and GluA2-lacking Ca2+-permeable AMPARs (CP-AMPARs), a subtype of AMPAR that has larger single channel conductance, in the hippocampus. We have further shown that this ketamine-induced CP-AMPAR expression enhances glutamatergic synaptic strength in hippocampal neurons, which allows animals to exhibit less anxiety- and depression-like behaviors. Our new findings further demonstrate that low-dose ketamine treatment can reverse disruptions in hippocampus-dependent fear memory and social behavior caused by chronic restraint stress (CRS) in mice. Research also shows that ketamine-induced restoration of impairments of AMPAR-mediated synaptic transmission and behaviors in stressed animals is associated with an increase in synaptic GluA1 expression in the hippocampus. Notably, the hippocampus is one of the key brain regions controlling social behavior and learning and memory. Moreover, an increase in hippocampal activity reverses stress-induced memory impairment, social dysfunction, and mood disorder-linked behaviors. More importantly, a recent study shows that the hippocampus is selectively targeted by low-dose ketamine. These existing data and our findings show that ketamine at the low dose rapidly induces the expression of CP-AMPARs in the hippocampus, which, in turn, enhances synaptic strength to reverse hippocampus-dependent behavioral dysfunctions in chronically stressed animals.

Prenatal Perceptions Mediate Link Between Pregnancy Intention and Caregiver Sensitivity

Juelle Ford, Vanderbilt University
NIMH
Poster 50
juelle.ford@gmail.com

Children born from unintended pregnancies, on average, experience less warm, responsive interactions with their caregivers (Claridge et al., 2017) and are more likely to be maltreated (Guterman, 2015) compared to children from intended pregnancies. Exploring pathways from pregnancy intention to later caregiving behaviors may yield important intervention targets relevant for children at risk for negative caregiving experiences and maltreatment. Participants in this study (n=290) were enrolled during their pregnancy (Mage=31.17, SD=4.89) and were followed longitudinally with their infants after birth. This sample self-identified as 85% White, 8% African American or Black, 1% Asian, 1% Native Hawaiian or Pacific Islander, 7% Hispanic or Latinx, and 5% selected "Other" (e.g., multiracial). Participants' perspectives about their pregnancy were assessed via survey and 70% (n=225) reported that their pregnancy was intended, while the remaining 30% (n=85) reported that their pregnancy was not intended. The Working Model of the Child Interviews (Zeanah et al., 1994), which assesses mental representations held about an individual's unborn child, was administered to participants during their pregnancies. To assess caregiver behavior, caregiver–infant dyads completed an 8-minute free play interaction when children were approximately 6 months old. Sensitivity and warmth were coded by trained raters from these interactions using the Parent-Child Interaction Rating Scales-Infant Adaptation (Bosquet Enlow et al., 2014; Sosinky et al., 2004). After accounting for covariates, we observed a moderate positive association between pregnancy intention and later caregiver sensitivity (β=.41, p=.003). Further, this association was partially explained by prenatal richness of perceptions of the child. Specifically, caregivers with intended pregnancies exhibited greater richness in their perceptions of the child during pregnancy (β=.20, p=.013), which subsequently was associated with more sensitive (β=.33, p=.001) and warm interactions (β=.27, p=.002) with their infants (see Figure 1). No association was found with the caregivers' prenatal by their acceptance of the child. We replicated prior literature linking pregnancy intention to caregiving quality. We also identified a potential mechanism explaining the association. Specifically, this study highlights the potential importance of prenatal mental representations of the child in shaping caregiver behavior. The results suggest that developing richer impressions of the child during pregnancy, especially among those who did not intend to become pregnant, may have downstream consequences on caregiving interactions. Overall, the study underscores the significance of understanding the psychological processes underlying caregiver behavior and the implications for early caregiving interventions that can be initiated prenatally.

Associations Between Resting-state Functional Connectivity of the Locus Coeruleus and Anhedonia Symptoms in Individuals with Depression

Gimarie Irizarry-Martinez, University of California, Irvine
NIMH
Poster 51
girizarr@uci.edu

Anhedonia is a transdiagnostic symptom associated with depression, reflecting a loss of pleasure. Dysfunction of the locus coeruleus (LC), a brainstem nucleus that is the main source of norepinephrine in the brain, may be one neural substrate of anhedonia. The LC responds to salient events and modulates arousal and memory through direct and indirect pathways via the basolateral amygdala (AMY) and hippocampus (HC). Prior studies of the neural substrates of anhedonia found decreased connectivity between reward-associated structures, such as the ventral tegmental area (VTA). However, the role of LC functional connectivity (FC) has not been studied. We hypothesize that decreased connectivity between the LC-HC and LC-VTA, and increased connectivity between LC-AMY will be related to greater anhedonia symptoms. Resting state fMRI data was analyzed from 63 participants (16 healthy controls, 47 individuals with depression; mean age: 22.9 years; range 18-37 years; 76% female). Seed-to-seed FC was calculated for LC-HC (rostral and caudal HC ROIs), LC-AMY (medial and lateral AMY ROIs), and LC-VTA. To assess anhedonia symptoms, we calculated an anhedonia score based on the Beck Depression Inventory (BDI). FC was compared between controls and individuals with depression, and anhedonia scores were correlated with FC. Sex was included as a covariate in analysis. Results: Compared to controls, individuals with depression had lower FC between LC and left caudal HC ($t=2.55$, $p=0.007$). Further, higher anhedonia scores were significantly correlated with lower FC between the LC and left caudal HC ($r=-0.22$, $p=0.04$) and a trend for the right rostral HC ($r=-0.15$, $p=0.11$). However, we did not find significant results for the LC-VTA and LC-AMY. Future directions will aim to stratify the sample into anhedonia subcategories to further characterize LC's neural signatures. Understanding neurobiological mechanisms of LC FC in depression could help develop targeted treatments for anhedonia.

Heterogeneity of Intersectional Discrimination Experiences Among Young Black Gay, Bisexual, and Other Men Who Have Sex with Men in the United States

Sarah Janek, Duke University
NIMH
Poster 52
sarah.janek@duke.edu

Authors: Sarah E. Janek, BSN, RN, ACRN,1 Wei Pan, PhD,1,2 Rosa Gonzalez-Guarda, PhD, MPH, RN, CPH, FAAN,1 Lance Okeke, MD, MPH,2 Tonia Poteat, PhD, MPH, PA-C,1 Marta I. Mulawa, PhD, MHS1,3

Affiliations:
1. Duke University School of Nursing
2. Duke University School of Medicine
3. Duke Global Health Institute

Background: Young Black gay or bisexual men, and other men who have sex with men (YBMSM), experience significant HIV and other sexual health inequities. Given the sociohistorical and ongoing context of discrimination in the United States, discrimination is increasingly recognized as an important social determinant of health in this population. YBMSM inhabit multiple intersecting social categories, though previous research has largely treated this population as a homogenous group experiencing discrimination due solely to racism and homophobia. In the proposed study, we aim to understand the heterogeneity of YBMSM's intersectional discrimination experiences through a latent profile analysis (LPA) that identifies subgroups of participants with distinct patterns of recent discrimination based on race or ethnicity, physical appearance, sexual orientation, and education or income level.

Methods: We analyzed the baseline data for a subsample of YBMSM, ages 18-29 and living without HIV (n = 266), from a large, NIH-funded study (R01MD013623). Discrimination experience in the prior 3 months was measured using the 9-item Everyday Discrimination Scale (EDS), ranging from 1 to 4 for each item, with a higher score indicating more frequent discrimination. A subsequent question asked participants to select all applicable reasons for their discrimination experiences (including race or ethnicity, physical appearance, sexual orientation, and education or income level). We conducted the LPA using the mclust R package to identify subgroups of participants with similar patterns of responses on four indicators comprised of their mean EDS scores for each of the selected discrimination reasons. The optimal number of profiles was identified by comparing models based on their Bayesian Information Criteria (BIC) and considering the substantive interpretation of the class profiles. We then examined descriptive statistics to characterize these profiles. We also used ANOVA and chi-square tests to examine significant differences among the mean EDS scores and demographics that differentiated the profiles.

Results: The LPA suggested that a four-profile model provided the best fit to the data. The largest profile was characterized by a low average recent EDS score (M = 1.70; SD = 0.65) with race and sexual orientation being the selected reasons among 92% of 155 participants. Two medium average EDS score profiles emerged, one with all four indicators selected by all 31 participants (M = 2.64, SD = 0.61), and the other 34 participants endorsing race or ethnicity, physical appearance, and education or income (M = 2.21, SD = 0.68). The highest average EDS profile (M = 2.85, SD = 0.58) was made up of 41 participants who selected race or ethnicity, physical appearance, and sexual orientation. Out of all the demographic characteristics, only insurance status differed significantly across profiles (p = 0.04). Most notably, only 58% of participants in the medium EDS profile with all four indicators represented were insured, compared to the other profiles that ranged from 79-83% insured.

Impact: This analysis provides a key foundation for future research to understand how discrimination varies among a population previously studied as homogenous in their experiences. By characterizing this heterogeneity, we hope that more research can focus on HIV and sexual health inequities by addressing multilevel discrimination from an intersectional discrimination lens, rather than targeting individual behaviors. We believe that this continued research will greatly contribute to the knowledge and mitigation of health inequities among YBMSM.

Conclusion: Although the discrimination experiences of YBMSM have often been thought to be restricted to racism, homophobia, or the intersection of the two, our LPA depicts the emergence of four distinct profiles, representing heterogeneity of intersectional discrimination among this population.

Examining the Relationship between Family Demographics and Engagement with Part C Early Intervention Services across Four US States

Mariela Jiménez, University of Massachusetts Boston
NIMH
Poster 53
mariela.jimenez001@umb.edu

Our aim was to outline potential barriers, if any, that exist in the engagement with Part-C early intervention (EI) services. To demonstrate said barriers, we examined rates of session attendance and cancellation across an ethnoracially, socioeconomically, and regionally diverse sample.

General linear model analyses were run to determine if specific demographic factors were significant predictors of rate of sessions held and/or cancelled. Race was found to be a significant predictor of cancellation rate, but not session rate. Number of children in the household predicted session rate, but not cancellation rate. State of residence predicted both session rate and cancellation rate. Neither ethnicity, income, nor parent education were significant predictors.

Diversity of KSHV Subtypes in People Living with HIV in a Large Urban Center in Dallas, Texas

Sheena Knights, University of Texas Southwestern Medical Center
NIMH
Poster 54
sheena.knights@utsouthwestern.edu

Human herpesvirus-8 (HHV-8), also known as Kaposi's sarcoma-associated herpesvirus (KSHV), causes Kaposi's sarcoma (KS) and other KSHV-associated disease (KAD). We previously described high KSHV seroprevalence and high KS incidence in a population of men who have sex with men (MSM) with HIV in Dallas, Texas; we now describe viral genetics in the same population.

We analyzed samples from participants recruited in 2 different studies, one enrolling MSM with HIV with and without KAD, and the other enrolling MSM with HIV and KAD. We measured KSHV IgG in serum using a combination of ELISA and a bead-based multiplex assay. Oral fluid samples of all individuals with KAD and seropositive individuals with no KAD were analyzed by RT-PCR to detect and quantify KSHV DNA. Samples with detectable KSHV underwent Sanger and/or next generation sequencing to determine K1 subtype.

Overall, 281 participants were recruited; 59 shed enough virus for K1 subtyping. Of these, 37 did not have KAD and 22 had KAD; all had KS. Table 1 describes the demographic characteristics of these participants. Notably, those with KS had lower median CD4 counts than those without KS ($p < 0.01$). All known K1 subtypes, except for D, were identified in this cohort, including the rare E and F subtypes. The latter, which has only recently been described outside of Africa, was identified in 6 individuals. Four participants had mixed infections with 2 or more KSHV subtypes (Figure 1). Figure 2 illustrates clinical presentations by KSHV subtype. Limitations in sequencing technology and study design permit no inferences on possible associations between KSHV subtype and KS onset or severity. We observed a larger proportion of subtypes B and F, typical of African populations, in participants with KS, than those with no KAD (8/27 subtypes detected vs 3/37). However, A and C were the most commonly identified subtypes in KS (19/27 subtypes in those with KS vs 32/37 subtypes in those without KS), including in advanced cases (i.e. T1 stage, 10/13).

In conclusion, we observed extreme diversity in KSHV genomes sequenced in a single institution in Dallas, Texas. Further studies are needed to better understand the relationship between viral genetics and KSHV epidemiology and disease risk in the southern U.S.

Increased Anxiety-like Behavior and Stress Responses in Adult Female Rat Offspring of Immune-Activated Dams

Monique Martinez, University of Arizona
NIMH
Poster 55
moniquem15@arizona.edu

Exposure to infection or other stressors during pregnancy can cause maternal immune activation (MIA). Resiquimod (RQ), a toll-like receptor 7 agonist, induces inflammatory responses and mimics viral infections. The current project investigates the degree to which late-gestation MIA with RQ impacts offspring development, anxiety-like behavior, and neuroendocrine function. Pregnant rat dams received a vehicle (saline) or RQ (1 mg/kg, s.c.) injection on gestation day 18. We assessed anxiety-like behavior using an open field test and measured plasma corticosterone (CORT) responses to restraint stress in offspring before puberty (postnatal days 23-28) and after puberty (9-10 weeks of age). In-utero MIA exposure did not affect offspring birth weights or early-life developmental milestones (i.e., the timing of eye opening and righting reflex). However, the female offspring of RQ-injected dams experienced a delay (~1 day) in vaginal opening, suggesting delayed pubertal onset. Before puberty, MIA did not affect open field or restraint CORT assessments. After puberty, RQ increased anxiety-like behavior ($F(1,13)=7.046$, $p=0.0198$). Specifically, the adult female offspring of immune-activated dams spent less time in the center zone ($p=0.0244$) compared to their controls. Additionally, restraint CORT concentrations tended to be higher in the offspring of RQ-injected dams ($F(1,12) = 3.133$, $p=0.1021$). These findings suggest that MIA leads to increased anxiety-like behavior and may dysregulate the hypothalamic-pituitary-adrenal axis in adult female offspring. Moreover, the data suggests that gonadal hormone changes during puberty may play a role in programming these sex-selective changes. These studies contribute to our growing understanding of the sex-selective consequences of MIA on offspring health.

Exploring Determinants of Psychiatric Genetics Research Participation Among Individuals of Latin and African Descent: A Mixed Methods Approach

Ogechi Onyeka, Baylor College of Medicine
NIMH
Poster 56
ogechi.onyeka@bcm.edu

Genetic factors are among the strongest established risk factors for internalizing problems. However, there remains a paucity of representation of individuals of Latino and/or African descent within psychiatric genetics research. Moreover, the consistently low participation rates of individuals of Latino and/or African descent in internalizing symptoms genetics research may call into question the generalizability of our current literature base. While concerns such as medical mistrust and mental health stigma are commonly discussed as contributing factors of this research disparity, acknowledging these factors alone has not narrowed the research gap. More probable causes may include culturally deficient recruitment strategies and limited interface with community stakeholders to develop research approaches that reflect the needs of the population under study. Investigative frameworks such as Community-Based Participatory Research (CBPR) are helpful approaches to draw from to best involve stakeholders in developing recruitment strategies with cultural humility. The current mixed method study used CBPR approaches to identify community-informed best practices for recruiting individuals of Latin and African descent in internalizing disorders genetics research, namely culturally informed determinants in participation. An exploratory, sequential mixed method research design was used to first investigate lived experiences of internalizing symptoms, the impact of culture, and perceptions of psychiatric genetics research among individuals of Latin and/or African descent via qualitative interviews. Next, emerging themes from the interviews were used to inform the development of a quantitative survey to explore patterns and relationships among these variables. Thirty interviews were conducted among individuals of Latin and/or African descent with self-reported internalizing symptoms (i.e., anxiety, depressive, obsessive-compulsive, and post-traumatic stress). Grounded theory coding and inductive thematic analysis revealed four key thematic dimensions: lived experiences and cultural influences, knowledge of psychiatric genetics research, barriers to participation, and willingness to participate. Several constructs identified from the interviews (e.g., research mistrust, stigma, family-based mental health beliefs) were then examined quantitatively (N = 206). Multiple regression analysis revealed that, when combined, family-based mental health beliefs, research mistrust, and stigma were significantly associated with attitudes towards psychiatric genetics research, $F(3, 202) = 17.997$, $p < .001$. Specifically, positive family-based mental health beliefs ($b = .31$, $p<.001$) and negative research mistrust ($b = .24$, $p<.001$) were significantly associated with positive attitudes of psychiatric genetics research participation. Findings were consistent with previous literature regarding barriers to participate in psychiatric genetics research among these populations, yet highlight the importance of understanding family context, culturally relevant language, and acknowledging individual lived experiences during recruitment.

K27 Polyubiquitination is a Sex-specific Regulator of Contextual Fear Memory Formation in the Hippocampus but not the Amygdala

Morgan Patrick, Virginia Tech
NIMH
Poster 57
morganbp@vt.edu

Females are 2-3 times more likely than males to develop post-traumatic stress disorder (PTSD), despite experiencing less traumatic events, leaving questions about the neurobiological mechanism that drives this sex difference in PTSD prevalence. Polyubiquitination is a process whereby multiple ubiquitin protein link to each other on a target substrate, often marking that substate for various cellular processes, of which protein degradation via the proteasome is the most well described. However, there are 8 different linkage sites at which polyubiquitin changes can form, most of which have not been studied in the brain. K27 polyubiquitination — in which ubiquitin link together at lysine 27 (K27) — is one such mark that has never been examined in the brain and, in general, little is known about the functional outcome of this polyubiquitination on a target substrate, though some evidence suggests it leads to protein degradation. Considering our recent evidence that some forms of polyubiquitination have sex-selective roles in the formation of fear-based memories for traumatic events, it is important to understand how these noncanonical polyubiquitin chains contribute to fear memory formation in the brain. Here, we found that K27 polyubiquitination was selectively increased 1 hour after contextual fear conditioning in the female, but not male, hippocampus, though neither sex showed changes in this polyubiquitin mark in the amygdala. Consistent with this, CRISPR-dCas13 RNA editing of the major ubiquitin gene, Ubc, to knockdown K27 polyubiquitination in the hippocampus selectively impaired contextual fear memory retention in the hippocampus of females, but not males, with no effect on either sex in the amygdala. However, surprisingly, our CRISPR-dCad13 manipulation caused a compensatory increase in K27 polyubiquitination in the amygdala, which occurred simultaneously with decreases in K63 and M1 polyubiquitination in females. Together, these data suggest that K27 ubiquitination has a sex-selectively role in fear memory formation in the hippocampus and may also control coordination of other polyubiquitin marks in the amygdala in females, but not males. These findings advance our understanding of molecular mechanisms of fear memory formation, which could aid the development of future sex-specific treatments for PTSD.

Developmental Shifts in Irritable Behavior Manifestation from Preschool to School-age: A Longitudinal Network Analysis

Erin Peterson, San Diego State University
NIMH
Poster 58
eopeterson@sdsu.edu

We charted how behavioral manifestations of irritability unfold from preschool- to early school-age (N = 497) using network analyses. Violent behaviors during and difficulty recovering from temper tantrums at preschool-age predicted widespread irritability symptoms at early school-age, suggesting important symptoms to target in early interventions.

Stigma and Sociocultural Variables Related to Latine Adolescents with a History of Suicidal Behavior: Preliminary Qualitative Data

Norka Polanco-Frontera, Ponce Health Science University
NIMH
Poster 59
npolanco@psm.edu

The study of stigma has been very limited among children and adolescents, especially Latine/Hispanic (L/H) youth. Mental health (MH) and suicide stigma (SS) have been identified as barriers for receiving treatment in the L/H community. There is a need to understand the association between mental health stigma (MHS), SS and suicide ideation (SI) among H/L youth with suicidal behaviors. The overall goal of the study was to gain a preliminary understanding, from a qualitative perspective, of the role of SS and MHS among L/H adolescents in Rhode Island (RI) and Puerto Rico (PR). In this descriptive and exploratory mixed-method study design conducted in PR and RI, 14 L/H adolescents (12–17 years) who experienced severe SI, had histories of suicide attempt, or had been hospitalized in the last 6 months were recruited. Participants first completed self-report questionnaires and then participated in a one-time semi-structured interview in person or via video conference. Recruitment placements were First Hospital Panamericano and Wellness Center in PR and Lifespan Hospitals in RI. All interviews were transcribed and coded. A deductive content analysis of the "suicide stigma" and "mental health stigma" codes was conducted. The following themes were identified in the adolescents' interviews in both sites: 1) being negatively labeled, 2) changes in others' behaviors, 3) perceptions about others' beliefs about mental health and/or suicidal behavior, and 4) adolescents' beliefs and decisions about disclosure. Similar to the team's previous findings, SS and MHS are related to the adolescents' experiences of being labeled, observing others' behavioral changes, or being avoided by people close to them. Also, the experiences of talking about suicide experiences and MHS are limited were not promoted in participants' families. Additional case analyses are required for a better understanding. The research team confronted limitations related to delay in the IRB and discrepancy between Expected and actual numbers of potential participants.

Effects of Recruitment Messaging on Ethnic/Racial Minority Enrollment in an RCT for Prenatal Insomnia: An Experimental Approach

Carolyn Ponting, University of California, San Francisco
NIMH
Poster 60
carolyn.ponting@ucsf.edu

Pregnant Latinx and Black people enroll in randomized controlled trials (RCTs) for sleep disorders less often than their non-Latinx white counterparts. Using data from a nationwide recruitment campaign for an RCT evaluating digital cognitive behavioral therapy for prenatal insomnia, we tested whether a recruitment message that identified a racial/ethnic disparity in sleep quality (sleep disparities message) would increase the proportion of participants who engaged in study screening, compared to a recruitment message without identified ethnic/racial disparities (standard message). Using simple randomization, pregnant people (n=203,664) were assigned to receive a sleep disparities message or standard recruitment message via email. In total, 1,782 pregnant people opened the recruitment emails. We used chi-square tests to compare the proportions of emails that led to study screening outcomes between the two email message conditions. The chi-square tests revealed that emails with a sleep disparities message resulted in significantly fewer visits to the screening website $X2$ (1, N = 1,782) = 8.83, p = .003 and fewer completed screeners $X2$ (1, N = 1,782) = 4.92, p = .026 than emails with a standard message. Additional analyses showed that, among people who completed a study screener, more Latinx and Black pregnant people received an email with a disparities message (38%) compared to a standard message (33.2%). However, results of a logistic regression detected no statistically significant interactions between race/ethnicity and message type on the probability of a completing a study screener. Implications for future perinatal recruitment messaging studies are discussed given the ongoing need to diversify CBT-I trials.

Prenatal Substance Use During the COVID-19 Pandemic: Exploratory Analyses

Marco Ramirez Gonzalez, Washington State University
NIMH
Poster 61
m.ramirezgonzalez@wsu.edu

During the COVID-19 pandemic, many measures were implemented to contain the spread of the SARS-CoV-2 virus. These measures, such as social distancing/isolation were linked with the increase in psychological stress, anxiety, and depression, as well as a decrease in overall quality of life. Mothers were not exempt, as women in maternity wards experienced lower levels of social and professional support due to the restrictions in place. Additionally, maternal substance use has increased since the start of the pandemic, for both pregnant and postpartum women. This project compared substance use scores on the ASSIST across two timepoints, one prior to COVID-19 and the other during the pandemic. Substances that were found to be significantly different across the two timepoints were subject to additional analyses to determine their relationship with a variety of maternal mental health measures.

Exploring PrEP Stigma Homophily and PrEP Conversations Among Latinx Men Who Have Sex With Men (LMSM) in South Florida

Edda Rodriguez, University of Miami
NIMH
Poster 62
e.rodriguez6@miami.edu

Introduction: In the United States (US), minorities are disproportionately impacted by human immunodeficiency virus (HIV). This impact is greater for individuals at the intersection of multiple minoritized identities, such as Latinx men who have sex with men (LMSM). For LMSM in South Florida, their vulnerability is increased due to the region's high HIV burden. South Florida is a US HIV epicenter, with the majority of cases occurring in Latinx people. Pre-exposure prophylaxis (PrEP) is a once daily oral pill or bimonthly injection that is 99% effective at preventing HIV transmission through sex. However, LMSM face numerous barriers to PrEP initiation and maintenance, including PrEP stigma. PrEP stigma is a multilevel barrier that impacts how individuals, community members, and PrEP-eligible individuals view PrEP. The negative sentiments tied to PrEP stigma hinder PrEP conversations, knowledge, and use.

Purpose: This poster explores the relationship between PrEP stigma and the frequency at which LMSM have PrEP conversations with members of their friendship network. Addressing the disproportionate HIV burden experienced by LMSM requires identifying and addressing barriers to prevention and care. Friends are a trusted source of health information, which may be accurate or inaccurate, making PrEP stigma within friendship networks particularly harmful.

Methods: From February 2022 to August 2023, we recruited networks of LMSM friends (N=194; N=67 networks). They provided information about their sexual behaviors, HIV prevention behaviors, and likelihood to discuss these topics with their friendship network members. Information regarding self-perceived PrEP stigma was used to create a stigma score for each respondent. Subsequently, a PrEP stigma homophily score was created for each friendship dyad. The homophily score was ascertained by taking the absolute difference between the friends' individual stigma scores, with lower values indicating greater PrEP stigma homophily. The relationship between PrEP stigma homophily and PrEP discussions was explored using a multiple regression quadratic assignment procedure correlation (MRQAP) test.

Results: Individuals with discordant PrEP stigma scores were less likely to have had PrEP conversations with their network members in the 6 months before their interview. Specifically, as PrEP stigma homophily scores increased, the likelihood of PrEP conversation decreased (B= -0.044, p=.046), such that discordant pairs were less likely to discuss PrEP than individuals who were similar in their PrEP stigma scores. However, this relationship was not seen when exploring participants' likelihood to have PrEP conversations or encourage PrEP use in the future.

Discussion: Social network methods are an important tool for identifying who LMSM discuss PrEP with, which is critical in improving equitable access to PrEP for HIV prevention. Our findings indicate that LMSM are speaking to individuals with PrEP views similar to their own. This may allow harmful stigmas to be reinforced, forming a cascading loop that decreases an individual's likelihood to engage in care.

Conclusion: These findings indicate that educating one network member is not enough to mitigate PrEP stigma; thus, network approaches should be utilized. Prevention scientists can leverage this information in the development of social network-based interventions that improve HIV prevention knowledge and acceptance. To gain a deeper understanding of this relationship, we are launching a longitudinal RCT that uses network-based approaches to engage LMSM with varying PrEP beliefs and PrEP knowledge. This RCT seeks to enhance PrEP use, aid in the reduction of HIV disparities, and provide insight on ways to dispel PrEP stigma.

Ethical Considerations of Data Sharing Policies in Neuroscience Research: A Case Study on Data Sharing Practices in Autism Research

Zuzana Skvarkova, Baylor College of Medicine
NIMH
Poster 63
zuzana.skvarkova@bcm.edu

The NIH Data-Sharing Policy requires that funded researchers share their data. Over the past two decades, various scientific communities, from genomics to neuroimaging, have shown that data sharing can reduce costs, drive innovation, and deepen scientific understanding. Advocates of data sharing argue that broader data availability can accelerate scientific progress and potentially promote equity within the scientific community. However, despite these potential benefits, the scientific field has consistently struggled with the challenge of recruiting diverse populations for studies, a problem that has persisted over the years. This lack of diversity in research participation has often led to inequities in scientific findings and their application, particularly in marginalized communities. Without diverse representation in research, the data being shared may not fully capture the range of experiences and outcomes across different populations, thereby perpetuating existing disparities. Despite recent initiatives aimed at addressing these disparities and enhancing diversity in participant recruitment, many studies still fall short of achieving genuinely inclusive representation. Given these persistent challenges, it is crucial to not only assess whether the benefits of data sharing outweigh the potential drawbacks but also to critically examine who truly benefits from these practices and how they affect the communities being studied. In autism research, where the population is highly heterogeneous, inclusive participant recruitment is critical to accurately reflect the spectrum of the condition. As data sharing becomes mandatory across NIH-funded studies, it is essential to consider the impact of these practices on the quality and equity of research outcomes and to understand community perspectives on data sharing. This poster presents preliminary findings from a diversity supplement under the BRAINshare Project (R01MH126937), focusing on the ethical considerations of data sharing in autism research. Through semi-structured interviews with key stakeholders, including parents of children with autism and autistic adults, three predominant ethical concerns emerged: informed consent, data ownership and control, and privacy. Additionally, the values of autonomy, respect, and transparency were highlighted as crucial in guiding these ethical considerations. By addressing these ethical challenges, researchers and funding organizations can ensure that data-sharing practices are both inclusive and respectful of participants' rights and preferences, ultimately fostering a more just and representative research environment.

Exploring the socio-ecological environment on the Malkia Klabu program for adolescent girls and young women in Tanzania

Camila Solorzano Barrera, University of California, San Francisco
NIMH
Poster 64
camila.solorzanobarrera@ucsf.edu

Authors: C. Solorzano-Barrera, A. Mnyippembe, J. Msasa, J. Allan, L. A. Sheira, C. Smith, E. Katabaro, J. X. Liu

Drug shops can improve access to adolescent sexual reproductive health (SRH) products, but how shopkeepers choose to promote and display SRH products may be influenced by perceived social stigma. Socio-cultural and structural influences can lead adolescent girls and young women aged 15-24 (AGYW) to face biased treatment from shopkeepers, avoid seeking SRH services, and compound access to an already disproportionately affected population by HIV infection and unintended pregnancy in sub-Saharan Africa. Our cluster-randomized trial (NCT05357144) in Tanzania, of about 150 drug shops enrolled across 41 wards (21 intervention, 20 control), tests the effectiveness of a girl-friendly program offering opt-out HIV self-testing (ST) kits and free SRH products to AGYW upon request at private drug shops (ADDOs).

With 6 months of shop sales data and observations of shop characteristics (i.e., shop structure, product placement and visibility), we used categorical predictor variables of HIVST kit visibility and SRH products placed in three locations within the shop interior walls (front, side, and back) along with the corresponding monthly total SRH products and HIVST kit sales per shop-month as the responsible variable. Each categorical predictor related to shop placement had three levels based on the recorded shop observations of the SRH products by month: not visible at all in that placement, placement visibly changed, and always visibly placed in that location. Ultimately, we ran one zero-inflated mixed model, accounting for health catchment area random effects and controlling for seasonality, study arm, and region to test our hypothesis: SRH products (condoms, oral and emergency contraceptives, pregnancy tests) and HIVST kits physically placed in visible locations within shops can affect young women's product uptake.

From June to November 2023, ADDOs with HIVST kits always visible sold a monthly median of 8 (IQR: 2,32) products, while shops that did not have kits visible at all sold 2 (IQR: 0,8) products per month. Shopkeepers that always visibly displayed their HIVST kits had 1.49 (95% CI: 1.40, 1.57) times as many mean counts of products distributed to AGYW compared to shops with no HIVST kits visible at all. SRH products placed on the side walls within ADDOs had 1.64 (95% CI: 1.57, 1.71) times as many mean products distributed compared to those that did not place the SRH products on the side walls at all within the shop-month. Consistent, visible product placement within shops may increase the saliency of SRH products and HIVST kits, resulting in more AGYW sales and engagement. Monitoring more socio-ecological influences

like product placement can contribute to understanding important implementation details for facilitating access to critical prevention services.

Higher Inflammatory Proteins Predict Future Depressive Symptom Severity Among Adolescents with Lower Emotional Clarity

Auburn Stephenson, Temple University
NIMH
Poster 65
auburn.stephenson@temple.edu

Background: A growing body of work has implicated inflammation in the pathogenesis of depression. As not all individuals with heightened levels of peripheral inflammation develop symptoms of depression, additional work is needed to identify other factors that catalyze the relationship between inflammation and depressive symptoms. Given that elevated levels of inflammatory activity can induce a variety of emotional changes, the present study examined whether emotional clarity, the trait-like ability to identify, discern, and express one's emotions, influences the strength of the association between inflammatory signaling and concurrent and prospective symptoms of depression.

Methods: Community adolescents (N = 225, Mage = 16.63 years), drawn from a larger longitudinal project investigating sex and racial differences in depression onset, provided blood samples to determine peripheral levels of interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and C-reactive protein (CRP) at a baseline visit, along with self-report measures of emotional clarity and depressive symptom severity. Depressive symptom severity was assessed again at a follow-up visit approximately 5 months after baseline.

Results: Hierarchical multiple regressions detected a significant interaction between inflammatory markers and emotional clarity on future depression severity, controlling for baseline depressive symptoms. Specifically, among adolescents with low levels of emotional clarity, higher IL-6 and CRP levels were significantly associated with greater future depression severity.

Conclusions: These results indicate that low emotional clarity and high inflammatory signaling may jointly confer risk for prospective depressive symptom severity among adolescents. Therapeutic interventions that improve emotional clarity may reduce risk of depressive symptoms among adolescents with low-grade peripheral inflammation.

Whose Depression are we Measuring? A Holistic Approach to Understanding Black Women's Health

Kanetha Wilson, Kaiser Permanente Georgia, Center for Research and Evaluation
NIMH
Poster 66
kanetha.b.wilson@kp.org

Background: Black women's health is not fully understood. Mechanisms underlying barriers to understanding include spuriousness in datasets, confounding between race and SES measures, and biopolitical meanings often included in health measurement. To begin addressing these barriers, this study uses a mixed methods approach to paint a more comprehensive picture of Black women's health. Specifically, the study examines interrelationships over time between physical health outcomes (e.g., body mass index [BMI]) and mental health outcomes (e.g., depression/anxiety diagnoses) within a closed health system. The context of the Atlanta region adds to the richness of data and findings given the large Black population and Black middle class in the region.

Methods: Data from this two-aim study consist of electronic health records (EHR) and transcribed semi-structured interviews from Black women members of Kaiser Permanente Health Plan of Georgia (KPGA). Additionally, Census-based data were linked with EHR. The first data-only aim includes statistical and geographical analyses using records from January 2012 to November 2023. This aim includes data from over 142,000 Black women. Data are analyzed at the yearly level, such that women can be represented only once each year. Socioeconomic stats (SES) is measured at the neighborhood (census tract) level. Location and sample size allow for the creation of neighborhood racial composition by median income level variables that can measure predominantly Black (>50%) neighborhoods both below and above median household income. The second aim includes data collection from semi-structured, 1- to 2-hour long qualitative interviews using a sample stratified by BMI category and neighborhood median income. To date, 8 of 20 interviews have been completed and transcribed. Presented here is an overview of descriptive and preliminary findings from both aims of the study.

Results: Results are broken down by age groups. Descriptive statistics indicate that neighborhood context may matter for some BMI categories. For instance, we observe the lowest rates of obesity (and highest rates of normal BMI) in women who live in areas over 50% White and above median income. Women in over 50% Black, below median income neighborhoods have higher rates of obesity class II across age groups. Neighborhoods above median income have higher rates of depression, yearly. Moreover, the lowest yearly depression rates are mostly observed among women living in over 50% Black, below-median income neighborhoods. Other patterns that emerge are increasing BMI with age, which tends to be consistent within existent literature. Multivariate analyses are currently being conducted to assess the significance of these variations. Interview data indicate important variations that may be missing when personal level factors are unavailable in EHR. Preliminary analysis of interview data point the following areas of exploration: 1) the role of occupation, including minority taxes associated with service and

care work; 2) the stress of heavy or primary financial responsibility, exacerbated by caregiving; 3) the need to redefine how we evaluate the body and weight; and 4) the need to understand how Black women express distress while feeling limited freedom to express raw emotions.

Conclusions: EHR and other secondary data are incomplete without including the words of Black women to better understand their health outcomes. Mapping further advances our understanding of how context shapes the health and lives of Black women.

Functional Characterization of Ultraconserved Elements in Neuronal Cell Types: Investigating Enhancer Activity and Cell-Specific Gene Regulation Using CRISPRi

Mark Youssef, Mount Sinai and Icahn School of Medicine
NIMH
Poster 67
mark.youssef@mssm.edu

Ultraconserved elements (UCEs) are highly conserved genomic regions associated with key regulatory regions of the genome, but their precise functional roles remain poorly understood. Previous research has focused on UCEs in model organisms like mice, where their deletion has been linked to abnormalities in brain structure and neuron populations. Little research has been conducted on their roles in human neuronal cells, leaving significant gaps in understanding how UCEs regulate gene expression in a cell type-specific manner within distinct human neurons.

We employed promoter-capture HiC with UCE-specific probes to identify their interacting regions within human stem cell-derived excitatory (iGluts) and inhibitory neurons (iGABAs). Combined with H3K27ac and chromatin accessibility data, we identified 21 UCE-gene pairs where the UCE is predicted to have enhancer activity, some potentially cell-type specific regulatory roles. To validate these findings, we designed gRNAs targeting a subset of UCE regions for CRISPR interference (CRISPRi) in iGluts and iGABAs and assessed their impact on predicted gene expression using qPCR.

Results showed that inhibiting certain UCEs led to reduced expression of predicted target genes, supporting their role as enhancers with cell type-specific effects. Unexpectedly, some instances of UCE inhibition resulted in increased gene expression, possibly due to more complex regulatory mechanisms than previously understood.

These findings expand our understanding of UCEs' specificity as regulatory elements, demonstrating their enhancer functions across neuronal subtypes with context-dependent effects. This adds complexity to UCE research, highlighting their selective enhancer functions in specific neuronal populations and contributing to broader insights into gene regulation during neurodevelopment.

Neural Mechanism of Prism Adaptation Therapy is Enhanced with Electrical Stimulation

Fisayo Aloba, Emory University
NINDS
Poster 68
oaloba@emory.edu

Background: Prism adaptation therapy (PAT) is a behavioral task used to evaluate visuomotor plasticity, and is an effective treatment to reduce left visuospatial neglect and improve visuo-motor function. Prism adaptation therapy modulates the processing of spatial cognitive information. However, the cortical plasticity mechanisms related to the behavioral effect of PAT are poorly understood. Non-invasive sensorimotor stimulation (estim) upregulates corticomotor excitability and is used as a therapeutic adjunct in motor training. Additionally, it has been shown to improve representation stage of processing spatial cognitive information. The feasibility, interactive effects, targeted neural substrates, and mechanism of combining PAT with estim (PAT+Stim) for the treatment of left visuospatial neglect are not known.

Objective: We evaluated spatial-motor treatment strategies that combine PAT+Stim and elucidated their effects on corticomotor excitability in the bilateral upper and left lower limb.

Methods: Fifteen young, able-bodied individuals (YAB) (18-35 years) participated in this study. Before and after PAT, we evaluated behavioral aftereffects of PAT and corticomotor excitability using motor evoked potential (MEP) amplitudes elicited in response to single and paired-pulse transcranial magnetic stimulation, delivered to M1 correlates of the left upper and lower limb.

Results: Both PAT+Stim and PAT+ShamStim (i.e., control) showed significant sensorimotor aftereffects. However, YAB suprathreshold MEP amplitude increased in the left first dorsal interosseus (FDI) and LTA and LSOLEUS in the PAT+Stim condition compared to PAT+ShamStim condition.

Conclusion: Although both PAT+Stim and PAT+ShamStim had significant behavioral aftereffects, PAT+Stim alone increased intracortical excitability in M1.

Significance: PAT with estim may enhance the model of rehabilitation of post-stroke SN compared to traditional PAT alone.

A Vault Bionanoparticle-Encapsulated Frataxin Gene-Targeted Histone Demethylation for Contracting GAA Repeats in Friedreich's Ataxia

Rhyisa Armbrister, Florida International University
NINDS
Poster 69
rarmbris@fiu.edu

Friedreich's Ataxia (FRDA) is the most prevalent form of recessive ataxia caused by the expansion of GAA repeats in the first intron of the frataxin (FXN) gene, leading to FXN gene silencing. No effective treatments for FRDA are available. Our previous studies have unveiled that temozolomide (TMZ), which can induce alkylated DNA bases that are predominantly repaired by the DNA base excision repair (BER), preferentially causes contractions of GAA repeats at the FXN gene in FRDA patient lymphoblasts and transgenic mouse cerebellar neural cells. We further revealed significant inhibition of H3K9 methylation (H3K9me) by TMZ, leading to decreased H3K9 trimethylation (H3K9me3) and increased H3K9 acetylation (H3K9ac) on the expanded GAA repeats in FRDA neural cells. This spurred the development of a bioengineered major vault protein (MVP) system encapsulating the FXN gene-targeted CRISPR/dCas9-KDM4D sgRNA-protein complex. This innovative approach facilitates the direct delivery of histone demethylase to the FXN gene, inducing demethylation of H3K9me2/3 and BER-mediated GAA repeat contraction. Given the natural occurrence of vaults in the central nervous system, our engineered MVP protein nanoparticles hold promise for traversing the blood-brain barrier and delivering specific proteins in a gene-targeted manner. Our study will uncover a novel paradigm, elucidating the synergistic interplay between CRISPR/dCas9-mediated FXN gene-targeted histone demethylation and DNA repair in mediating GAA repeat contraction in FRDA. This pioneering work will introduce the first human natural nanoparticle, vault-mediated FXN gene-targeted platform to disrupt heterochromatin and induce DNA repair-mediated contraction of expanded GAA repeats in FRDA, heralding a new era in FRDA treatment.

Exploring the Pathophysiology of Cognitive Dysfunction after Combination of Traumatic Brain Injury and Cortical Spreading Depolarization

C'Asia Bishop, University of Cincinnati
NINDS
Poster 70
bishopc3@mail.uc.edu

Please see poster.

Associations Between Perinatal HIV-related Risk Factors and Select Serum Polyunsaturated Fatty Acid (PUFA) Levels among Ugandan Children and Adolescents

Vanessa Cardino, Michigan State University
NINDS
Poster 71
cardinov@msu.edu

Authors: Vanessa N. Cardino, Selin Sergin, Jenifer I. Fenton, Sarah K. Zalwango, Amara E. Ezeamama

Objective: To determine if fatty acid (FA) levels differ by adolescent status and quantify the relationship between polyunsaturated fatty acid (PUFA) levels and perinatal HIV-related factors among Ugandan children and adolescents.

Methods: 243 school-aged children (6-10 years old) and 383 adolescents (11-18 years old) were recruited in Kampala, Uganda. Baseline serum samples were obtained and methylated to quantify FA using gas-chromatography mass-spectroscopy. Perinatal HIV infection/exposure and IPA exposure status were established from medical records. Descriptive statistics were used to analyze differences in FA levels by adolescent status, and multivariable linear regression analyses were performed to relate risk factors to select PUFA levels in each youth group.

Results: Adolescents had higher saturated FA (55.3% v. 43.4%) and monounsaturated FA (21.2% v. 7.2%) and lower n-6 (20.8% v. 46.4%) and n-3 (2.5% v. 2.9%) PUFA levels than children (all $p < 0.05$). Relative to children HIV unexposed uninfected (HUU), children with perinatal HIV infection (PHIV) had unfavorable FA levels (higher T:T ratio and Mead acid) with variations by IPA exposure type. Specifically, FA profile was worse for children PHIV with no IPA and combination ART (cART) exposure, but nevirapine+zidovudine+lamivudine (NVP+ZDV+3TC) exposure was associated with a favorable FA profile among children PHIV and children HIV exposed uninfected (HEU). Among adolescents, increasing age was associated with a more favorable FA profile. Overall, relative to adolescents HUU, adolescents PHIV had lower EPA levels, but FA levels varied further by IPA exposure type. Specifically, adolescents PHIV with no IPA exposure had lower linoleic acid and EPA levels and those with cART exposure had lower n-3 PUFA levels, but adolescent PHIV exposed to NVP±ZDV had more beneficial FA levels (all $p < 0.05$).

Conclusions: Adolescents are more vulnerable to low PUFA levels than children, but their levels increase with age. Overall, PHIV and HEU status are associated with low levels for some n-3 and n-6 PUFAs. However, the relationship between perinatal HIV status and FA levels varies by adolescent status and IPA exposure type. Additional studies examining the contributory role of IPA exposure type are warranted.

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Postnatal Development of Vasculature in the Hippocampal Neural Stem Cell Niche

India Carter, The Ohio State University
NINDS
Poster 72
carter.1666@osu.edu

Adult neurogenesis is the process of creating new neurons in adulthood. It is observed in many mammalian species and occurs in two main areas of the brain: the subventricular zone and the dentate gyrus (DG) of the hippocampus. The DG, in particular, has especially dense vasculature. DG neural stem cells (NSCs) along with their immediate progeny, intermediate progenitor cells (IPCs), exist in close proximity to these local blood vessels during adulthood. This unique relationship is believed to support the process of neurogenesis in several ways, such as providing NSCs access to circulating support molecules, like growth factors, and providing scaffolding for progenitors to migrate tangentially in the DG. Though the proximity of NSCs and IPCs to blood vessels in adulthood is well known, little is known about how it develops. To characterize the development of the proximity of NSCs and IPCs to blood vessels, we quantified the distance from radial glial-like NSC bodies and IPC bodies to the nearest blood vessel in mice from 2 to 9 weeks of age, an age range covering the formation of the DG cell layers up to adulthood. We used immunofluorescent phenotypic markers to identify NSCs, IPCs, and endothelial cells in wildtype mice perfused at 2, 3, 5, and 9 weeks of age. We found that there was a progressive reduction in the distance between NSC bodies and the nearest blood vessel from 2 to 9 weeks of age, and the same developmental pattern was true for IPCs. Our results suggest that the proximity between NSCs and IPCs with vasculature is not a preserved feature from early development, but is instead one that arises de novo during postnatal maturation. Additionally, these results imply that the DG neurogenic vascular niche is not finished developing until adulthood. Further, we are characterizing the DG vascular niche in mice at 2, 3, and 9 weeks of age by using EZ clear, a tissue clearing protocol, and IMARIS imaging software to create 3D renderings of the vasculature at each developmental time point. Additional investigations into the development of the DG neurogenic niche and the surrounding vasculature will shed light on the mechanisms that preserve neurogenesis into adulthood.

Elucidating the Role of Reactive Astrocytes on the Modulation of Blood-brain Barrier Dynamics through the STAT3-SERPINA3 Signaling Axis in Alzheimer's Disease

Rebecca Embalabala, Vanderbilt University
NINDS
Poster 73
rebecca.j.embalabala@vanderbilt.edu

Astrocytes are an integral component of the neurovascular unit (NVU) and are crucial for regulating blood-brain barrier (BBB) dynamics. In vitro studies have shown that the TNF-STAT3 signaling cascade induces astrogliosis, which leads to an enrichment of alpha 1-antichymotrypsin (SERPINA3). SERPINA3 (murine ortholog Serpina3n) is a secreted serine protease inhibitor that has emerged as a biomarker for various neurodegenerative diseases that can be detected through cerebral spinal fluid. In Alzheimer's Disease (AD), increased SERPINA3 levels correlate with increased disease severity. Recently, in vitro and ex vivo studies from our lab have shown that elevated levels of SERPINA3 secreted by reactive astrocytes leads to molecular signatures associated with BBB disruption. Here, we seek to explicate the molecular mechanisms underlying BBB dysfunction in AD modulated by the STAT3-SERPINA3 signaling axis that results from the cellular crosstalk between reactive astrocytes and brain endothelial cells.

Investigating Dynamics of Astrocyte Endfoot Formation during Development and Across Species

Raja Estes, Oregon Health & Sciences University
NINDS
Poster 74
estesr@ohsu.edu

Astrocyte endfeet are specialized processes that play vital roles in supporting neuronal health by maintaining the blood-brain barrier and regulating cerebral blood flow. How these processes develop and mature remains unresolved questions, due to limited in vivo techniques that allow visualization of endfeet. Further, endfoot development and angiogenesis occur in parallel, but mechanisms influencing endfoot formation along mobile and dynamic angiogenic vessels are poorly understood. Using in vivo imaging of astrocytes and vasculature in transgenic zebrafish, I am defining the full timecourse of astrocyte endfoot development from 2 days post-fertilization (dpf) to 10 dpf. Preliminary findings suggest that astrocytes begin establishing endfeet on vasculature at 2 dpf and maintain contact with angiogenic vessels as they refine their architecture over the course of development. Vasculature that is fully developed with a lumen and connecting vessels appear to be fully wrapped by endfeet, suggesting that astrocytes contact developing vasculature, then complete wrapping upon vessel maturation. To define evolutionarily conserved mechanisms of endfoot formation, I am also performing time course analyses of endfeet in both rats and mice during astrocyte development ranging from post-natal day(P) P6-P21 using immunofluorences and 3D reconstruction. Future studies will address the molecular determinants of endfoot formation in vivo using zebrafish and rodents. The findings from this project will fill a fundamental gap in the field by defining evolutionarily conserved mechanisms of astrocyte endfoot development along with generating novel tools to study glia-vascular interactions in vivo.

Exploring Heterochromatin Alterations as a C9orf72 FTD/ALS Hallmark

Raven Fisher, The Graduate Center of the City University of New York
NINDS
Poster 75
rfisher2@gradcenter.cuny.edu

Frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS) are fatal neurodegenerative diseases which form a disease continuum. Alterations in various epigenetic mechanisms such as histone post-translational modifications have been implicated in FTD/ALS. Hexanucleotide repeat expansions in chromosome 9 open reading frame 72 (C9orf72) lead to toxic dipeptide repeat proteins that are connected to distinct epigenetic signatures. Saccharomyces cerevisiae over-expressing the dipeptide repeat protein, Poly-Proline-Arginine, has revealed changes in histone marks, such as increases in transcriptionally active marks H3K9ac and H3S10ph, to be associated with C9orf72 pathology. These alterations are also present in fibroblasts from patients bearing C9orf72 expansions. Fibroblast models reveal additional decreases in a key heterochromatin mark, H3K9me3. Altogether, these findings suggest defects in transcriptionally silent heterochromatin to underlie neurodegeneration. Here, we explore how C9orf72 proteinopathy and histone modification changes affect heterochromatin.

Interference between similar memories increases the dimensionality and dispersion of recalled content

Julian Gamez, University of Oregon
NINDS
Poster 76
jgamez@uoregon.edu

Although countless memory studies have documented that similarity between memories produces interference and forgetting, relatively less is known about how memories adapt to interference so that they are successfully recalled. In rodents, high-dimensional neural representations have been shown to be critical for flexible behavior and cognition (e.g., Rigotti et al., 2013). Here, we tested whether memories adapt to interference through increases in the dimensionality of memory content. Human subjects (N = 120) extensively learned 6 face-scene associations. For half of the subjects, all of the scenes were from the same visual category and highly similar (e.g., 6 'libraries'; competitive condition); for the other half of subjects, each scene was from a distinct visual category (non-competitive condition). After learning, participants completed a recall task in which they were shown each face and typed a description of the corresponding scene. To quantify memory dimensionality, natural language processing was applied to the scene descriptions, yielding a semantic embedding for each scene (memory). Principal component analysis applied to these embeddings revealed that, compared to the non-competitive condition, participants in the competitive condition contributed relatively less to early components (1-5) and relatively more to later components (6-20), suggesting interference resulted in higher-dimensional memory representations. Additionally, k-means clustering (with K=6 categories) applied to the embeddings revealed that the distance to cluster centroids (dispersion) was significantly greater in the competitive condition compared to the non-competitive condition. Collectively, these findings support the idea that similarity between memories induces adaptive increases in the dimensionality of memory content.

Loss of m6A mRNA Readers in Zebrafish Model Impacts Brain Size Phenotypes Implicated in Autism

Gabriana La, University of California, Davis
NINDS
Poster 77
gnla@ucdavis.edu

Autism (ASD) is a complex neurodevelopmental condition encompassing a diverse range of phenotypes. ASD is highly heterogeneous in both phenotypic presentation and genetic predisposition, leaving much to be uncovered regarding its genetic etiology. Focusing on disproportionate megalencephaly (DM), a subphenotype of ASD where individuals have an enlarged brains disproportionate to their height, we identified two probands harboring cases of de novo mutations in two m6A-mRNA reader genes with no prior association with ASD — a duplication of YTHDF2 and a loss of function mutation in YTHDC1, respectively. Our preliminary data using zebrafish show that knocking out ythdf2 yielded smaller brain area and overexpression via injected transcripts resulted in larger brain area, recapitulating patient phenotypes. Following these results, we aimed to look towards other m6A mRNA reader genes, including ythdc1, ythdc2, ythdf1, and ythdf3, to see how loss of function may also impact head brain size phenotypes in our zebrafish model. Upon knocking out these genes via targeted CRISPR microinjections at the single-cell stage, we see significantly smaller head sizes in ythdc1 knockouts and significantly larger head sizes in ythdf3 knockouts at 3 days post fertilization. Additionally, we see potential development delay among ythdc1, ythdf1, and ythdf3 knockouts, indicated by reductions in body length compared to control, though further work is necessary to confirm this. Within the m6A mRNA pathway, readers interact with m6A-modified transcripts in the nucleus and cytoplasm, dictating the balance and timely export, translation, stabilization, and degradation of their target transcripts. We believe m6A-modified transcripts relevant to neurogenesis may be impacted by the loss or gain of function of any of these m6A mRNA readers. Our work will expand our mechanistic understanding of ASD etiology, potentially connecting m6A mRNA modifications as a contributor to this complex condition.

L-selectin Shedding Regulates Neutrophil Function in a Sex-dependent Manner After Spinal Cord Injury

Miranda Leal-Garcia, Texas A&M University
NINDS
Poster 78
mleal@bio.tamu.edu

During the acute phase of spinal cord injury (SCI), neutrophils infiltrate in large numbers and can exacerbate inflammation, promote secondary tissue damage, and worsen long-term functional outcomes. We have previously shown that augmenting the cleavage or shedding of L-selectin, an adhesion and signaling receptor on neutrophils, can reduce secondary injury and improve neurological recovery after SCI. However, it remains unclear how L-selectin shedding regulates neutrophil function following SCI. To determine the role of L-selectin shedding in neutrophil responses to SCI, we utilized L(E) mice, which express a non-cleavable version of L-selectin. We observed impaired long-term hindlimb recovery in L(E) female, but not male, mice compared to wild types (WTs). Interestingly, there was a marked reduction in spared white matter in L(E) mice from both sexes when compared to WT mice. Interestingly, there was a marked reduction in spared white matter in L(E) mice from both sexes when compared to WT mice. Using in vitro stimulation assays, we observed sex- and genotype-dependent differences in neutrophil effector functions in the absence of L-selectin shedding, including increased degranulation and ROS production in neutrophils from L(E) mice of both sexes. In vivo, we observed sex- and genotype-dependent differences in neutrophil accumulation at 3 and 35 days post-injury (dpi) in a thoracic contusion model of SCI. At 35 dpi, neutrophil accumulation was greater in L(E) females compared to WTs, but no differences were observed between L(E) and WT males. Our data demonstrates sex-dependent roles for L-selectin shedding in attenuating pathogenic neutrophil response after SCI.

Computational Modeling of Platelets and Thrombosis in Cerebral Aneurysm Treatment

Do Lim, University of Washington
NINDS
Poster 79
dolim@uw.edu

Here, we seek to improve the accuracy of hemodynamic modeling of cerebral aneurysms. The goal of this project is to predict the outcome of cerebral aneurysm treatment. This is significant due to the prevalence of cerebral aneurysms, their dismal prognosis when ruptured, and treatment failure rates (resulting in aneurysm recurrence and risk of either brain hemorrhage or need for retreatment) of up to 40%. Hemodynamic forces are thought to influence aneurysm treatment outcomes and can be simulated using computational fluid dynamics (CFD) methods, but such studies have not been widely accepted due to conflicting results. Traditional CFD analysis (termed "Eulerian" metrics) only studies the effect of blood flow on the vascular walls, largely ignoring circulating blood products, such as platelets, that initiate intra-aneurysmal thrombosis (termed "Lagrangian" metrics), which have a critical role in treatment outcome. Better prediction through a holistic approach combining both types of analyses could identify patients at risk for treatment failure, influencing pre-surgical decision-making.

This project builds on our ongoing NIH-funded expertise (via a renewal of R01NS105692) in the CFD modeling of cerebral aneurysms before and after treatment. We have developed an innovative method of incorporating novel Lagrangian metrics, such as residence time and shear history, into CFD simulations in with existing Eulerian hemodynamic metrics, to create a holistic approach to modeling the effects of aneurysm treatment. Feasibility studies have characterized the post-treatment hemodynamic environment, with special attention to platelet-representative particles that experience prolonged intra-aneurysmal residence time and low cumulative shear history within treated aneurysms. Previous in vitro studies of platelets in similar conditions demonstrate thrombosis in such environments, which would be advantageous after aneurysm treatment to develop a stable thrombus leading to aneurysm healing.

First, we will perform CFD simulations before and after treatment on a cohort of cerebral aneurysms whose treatment outcome (success or failure) is known. We will include both Eulerian and Lagrangian metrics to determine associations with treatment outcome. Second, we will use an established animal model of cerebral aneurysms, treated with commercially-available endovascular devices. We will perform CFD simulations, using a similar holistic model as the human aneurysm cohort, and investigate the relationship between Lagrangian metrics and treatment-related thrombosis on histological analysis. The final result will be an optimized CFD methodology and a set of Eulerian and Lagrangian variables predictive of outcome after cerebral aneurysm embolization.

Mice Sleep Less During the Wake Cycle After Repeated Closed Head Injury

Kyli McQueen, University of Arizona College of Medicine – Phoenix
NINDS
Poster 80
kylimcqueen@arizona.edu

Head injury can disrupt sleep, and repeated head injury may produce compounding effects. However, the cumulative effects of repeated closed head injury on sleep remains unclear. In our prior study, repeated closed head injury every other day indicated a possible conditioning effect on subsequent head injuries and sleep. In this follow-up study, we hypothesized that, either once or twice daily, closed head injury would disrupt sleep patterns, particularly during the mouse wake cycle, and effect sizes would be cumulative with subsequent injuries.

Male C57BL/6J mice (n=12) were randomly assigned to either once daily (ZT=3) or twice daily (ZT=3&6) weight drop head injury (Height: 94cm, Weight: 100g) allowing free head rotation daily for five consecutive days. Mice were anaesthetized and weight drop was administered upon normal respiration. Mice were immediately monitored for righting reflex recovery time and returned to non-invasive piezoelectric sensor sleep recording chambers. Sleep was recorded hourly from ZT=12 to ZT=2 and analyzed for sleep density, defined as sleep percentage per hour during the animal's wake cycle.

No cumulative effects on righting reflex times or sleep were observed across the week for single or repeated injury. The righting reflex times for the second daily injury were longer than the first injury of the day. A decrease in sleep density was seen at three days post-injury ($F(1,20)=52.816$, $p<0.001$) compared to baseline. Sleep density was unaffected by injury number on day three ($F(1,20)=0.375$, $p=0.547$). Further studies will explore injury parameters and interactions between repeated head injuries.

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The Impact of Increased Blood Pressure Variability and High Salt Diet on Cardiovascular and Neurovascular Outcomes

Perenkita Mendiola, Augusta University
NINDS
Poster 81
pmendiola@augusta.edu

Background: Increased blood pressure variability (BPV), independently from absolute blood pressure (BP), is a novel risk factor for cognitive decline and dementia. The current in-office doctor screening practices for single or averaged BP readings make BPV a commonly overlooked risk factor with poorly defined underlying mechanisms. Additionally, with worldwide excessive salt consumption, whether the comorbidity of a high salt diet (HSD) contributes to BPV and exacerbates cognitive decline is not known.

Aims: This study aimed to establish a novel murine BPV model and evaluate the impact of BPV on systemic BP (baroreceptor reflex) and cerebral blood flow (CBF) regulation. We tested the hypothesis that blood pressure fluctuations in BPV disrupt critical vascular mechanisms that regulate CBF (myogenic and functional hyperemia [FH] responses), impairing cerebral perfusion and leading to neurovascular dysfunction and subsequent cognitive decline.

Methods: Chronic cranial windows were established in middle-aged C57Bl6 mice and DSI telemetry was implanted for simultaneous in-vivo two-photon (2P) imaging of cerebral vasculature and BP measurements. Mice were then implanted with programmable pumps which turned on every 3-4 hours. This resulted in an infusion protocol of infusing 6-8 pulses/day with angiotensin II (Ang II) (18 μg/day) (BPV group) or saline (control group) for 25 days.

Results: The infusion of saline had no effect on BP. However, Ang II pulse infusions evoked transient BP increases (Δ43±4 mmHg, MAP) ($P<0.01$, n=8) and increased BPV index, calculated by the average real variability ($P=0.04$, n=12). Despite the robust transient increases in BP, BPV mice did not develop hypertension (24h MAP). Following a 25-day BPV protocol, mice displayed a decrease in bradycardic reflexes ($P=0.03$, n=8) and a decline in cognitive function (novel object recognition test [$P=0.01$, n=10]). All 2P studies were conducted at an average depth of 105±3.7 μm below the brain surface (~layer 1 and layer 2 of the somatosensory cortex), focusing on parenchymal arterioles with an average starting diameter of 19±0.6 μm. Data from 2P studies showed that parenchymal arterioles of BPV mice had greater myogenic responses compared to controls ($P=0.005$, n=9-15 runs). An increase in BP evoked a significant increase of functional hyperemia in parenchymal arterioles of controls ($P<0.01$, n=6-7). However, this pressure-induced effect was abolished in arterioles of BPV mice compared to controls ($P<0.01$, n=6-7). In a separate cohort of control or BPV mice, the infusion protocol was repeated with all mice receiving HSD (HSD: 4% NaCl chow + 1% NaCl drinking water, control+HSD or BPV+HSD [HSD+BPV]). There were no changes in 24-hour MAP in HSD mice ($P>0.85$, n=5).

In contrast, HSD+BPV developed sustained hypertension (increased 24-hour MAP) ($P<0.01$, $n=4$).

Conclusions: These data demonstrate that parenchymal arterioles participate in buffering of perfusion pressure (myogenic responses in controls). In addition, the data demonstrate that BPV alters mechanisms regulating CBF and BP, contributing to cognitive decline, and that HSD may exacerbate the detrimental effects of BPV on BP-regulating mechanisms. The findings of this study support the efforts calling for the inclusion of BPV measurements in current in-office BP screening during doctor's office visits. Ongoing studies are examining the comorbid effects of HSD+BPV on the cerebrovasculature and direct CBF changes in BPV and HSD+BPV mice.

Elucidating the Role of Vagal Signaling in CNS Reward Networks

Chris Phillips, University of Texas at Dallas
NINDS
Poster 82
captain13phillips@gmail.com

The vagus nerves convey appetitive and nutritive signals from visceral organs to the central nervous system (CNS), influencing food-seeking behavior by activating neural networks that regulate motivation, satiety, and reinforcement learning. Recent research has shown that right versus left vagus nerve stimulation (VNS) differentially activate midbrain dopaminergic reward nuclei, including the ventral tegmental area (VTA) and substantia nigra (SNc) (1). Here, we aimed to develop in-house, low-cost mouse VNS cuff electrodes to test if right VNS (r-VNS) and left VNS (l-VNS) differentially modulate dopamine dynamics in the nucleus accumbens (NAcc). We found that VNS induces physiological responses in anesthetized mice. We then tested whether VNS activates reward networks, by quantifying cFos expression in the VTA and NAcc. Lastly, we validated dopamine sensor use in freely moving mice during open-field reward consumption. These experiments are paving the way for experiments combining chronically implanted cuff electrodes with in vivo dopamine recordings.

Mitochondrial Network Dynamics During Microglia Surveillance and Phagocytosis

Alicia Pietramale, Dartmouth College
NINDS
Poster 83
alicia.n.pietramale.gr@dartmouth.edu

Microglia are the resident macrophages of the central nervous system. Their primary function is first, surveillance of the environment by continually extending and retracting their highly branched processes; and second, phagocytosis of debris from inflammation or injury. When microglia respond to a stimulus, drastic morphological changes are sometimes necessary to carry out these functions. It is known that inflammatory stimuli can shift the bioenergetics of cultured microglia, which coincides with a morphological change of mitochondria in microglia. However, it is unknown how mitochondrial dynamics change as microglia processes perform surveillance, phagocytosis, and respond to injury in the live, intact brain. To investigate microglia mitochondria, we generated a triple transgenic mouse with microglia and the mitochondria within microglia endogenously labeled with fluorescent markers. Cranial window surgeries and awake two-photon imaging were performed on these animals to determine the morphometrics and motility of mitochondria in microglia. We found that mitochondria are not uniformly distributed in the microglia processes; some processes containing many mitochondria, while others had very few. Surprisingly, most of the processes that engage in minute-to-minute surveillance do not have mitochondria. Likewise, as microglia respond to a laser lesion, the processes that immediately chemoattract to the lesion site do not have mitochondria. Rather, the mitochondria have a delayed arrival into the microglia processes responding to the lesion. This is the first real-time visualization of mitochondria in microglia in the live animal. We found that mitochondria are not localized to microglia processes performing homeostatic surveillance, nor are they found in microglial processes responding to acute tissue damage. These data establish the dynamics and morphometrics of microglia mitochondria in vivo and indicate heterogeneity of process function within a single microglia cell.

Multi-omics Analyses and Functional Synaptome Aberrations in C9orf72 ALS/FTD

Ashton Spillman, Barrow Neurological Institute
NINDS
Poster 84
ashton.spillman@barrowneuro.org

An important aspect of neuronal function and communication in the central nervous system is the maintenance and refinement of synaptic networks through the selective pruning of synapses, which occurs predominantly, but not exclusively, during development. Interestingly, these processes are also triggered in neurodegenerative diseases and are thought to be responsible for the observed loss of synapses in these disorders, which include Alzheimer's disease, frontotemporal dementia (FTD), and other related dementias. Astrocytes and microglia are known to contribute to synaptic pruning during development and thereby play an important role in activity-dependent synapse remodeling. Numerous pathways have been implicated in this process, including the activation of the complement cascade, which is proposed to prime the synapses for removal by exposing so-called 'eat me' signals onto neuronal synapses. Here, we sought to uncover 'eat me', but also 'spare me' signals deposited onto neuronal synapses in C9ORF72 amyotrophic lateral sclerosis (ALS)/FTD using patient-derived induced pluripotent stem cells (iPSC), differentiated into cortical neurons, in addition to postmortem autopsy tissue from C9ORF72-ALS/FTD patients. To enrich for synaptic proteins, a series of centrifuge-based fractionations were performed to obtain a synaptosome preparation including fractions containing both pre- and post-synapses, as well as an enriched post-synaptic fraction. Synaptosome preparations were generated from iPSC-cortical neurons and postmortem frontal cortex tissue samples. We validated synaptosome preparations from iPSC neurons and confirmed enrichment of presynaptic and postsynaptic proteins in the appropriate synaptosome fractions. At the same time, we generated synaptosomes from 4 healthy, non-neurological control and 6 C9ORF72 ALS/FTD frontal cortex autopsy brain tissues. The purified synaptosomes underwent deep expression proteomics profiling, which revealed, on average, 550 proteins/sample and 60,000 peptides/sample. Of those, 83 proteins were differentially abundant in C9ORF72-ALS/FTD synaptosome, with 23 being more abundant and 60 being less abundant. Among the 23 more abundant proteins were potential biomarkers for ALS/FTD, including TMEM41B, PTP4A3, WRN, MTFMT, HOXA2, KCNT1, SPRED2, and VWF. Gene set enrichment analysis revealed positive enrichment for (1) synapse assembly/organization, (2) neurogenesis, and (3) neurotransmitter receptors and postsynaptic signal transmission, while negative enrichment was found in immune response pathways. Interestingly, ingenuity pathway analysis revealed a significant inhibition of the EIF2 signaling pathway, while there is increased activity in glutamatergic receptor signaling pathway, with the most upregulated proteins GABRA1, GABRA3, and GABAa receptor gene variants. Comparison of these proteomics data to recently published snRNA sequencing data from our laboratory revealed some overlapping aberrantly expressed gene expression, but also highlighted the discrepancies frequently found between RNA and protein analyses within the same tissue samples. Ongoing studies are aimed at

validating the ex vivo patient tissue -omics data using the iPSC-cortical neuron synaptosome model, followed by mechanistic assessments.

Non-canonical Roles of Cell Adhesion Molecules in Presynaptic Patterning

Jada Summerville, Albert Einstein College of Medicine
NINDS
Poster 85
jada.summerville@einsteinmed.edu

Synapses are an integral part of the proper function of neural circuitry. Yet, how synapses are formed, matured, and maintained has remained elusive. Cell adhesion molecules (CAMs) have been implicated as important players in synaptogenesis, as their extracellular interactions with their binding partners on a partner cell can induce synapse assembly. However, how these extracellular interactions are transduced into intracellular signaling to form a synapse is less understood. Using C. elegans, we have identified a CAM, SYG-2, that may have intracellular roles in synapse assembly independent of its known trans-synaptic roles. We have found that deletion of SYG-2 results in a disruption in presynapse number, spacing, and active zone size in the dorsal motor neuron DA9. Loss of its binding partner, SYG-1, results only in a disruption in synapse spacing, suggesting that these binding partners do not have a one-to-one functional relationship. We have found that SYG-1 and SYG-2 are both expressed in the body wall muscle and excitatory neurons, yet only SYG-1 is expressed in inhibitory neurons. We have also confirmed that SYG-2 functions cell-autonomously from the presynaptic cell, DA9. Interestingly, we have found that over expression with the intracellular domain of SYG-2 alone is sufficient for inducing presynaptic assembly. Using CRISPR to mutate candidate motifs of the intracellular domain of SYG-2, we will elucidate which domains are required for SYG-2's function and possible interactions with other proteins, thus constructing the pathway in which SYG-2 operates for presynaptic assembly. These experiments will provide insight for the possible underlying mechanism of SYG-2 human ortholog NEPH2/KIRREL3, which has been implicated in intellectual disabilities.

Kilohertz Transcranial Magnetic Perturbation (kTMP): A New Subthreshold Method to Modulate Cortical Excitability

Katheryn Thayer-Pham, University of California, Berkeley
NINDS
Poster 86
thayerpham@magnetictides.com

Authors: Christina M. Merrick, Katheryn Thayer-Pham, Cidnee Luu, Philipp Reber, Saumya Singh, Ian OKidhain, Angel Peterchev, Daniel Sheltraw, Richard B Ivry, Ludovica Labruna

Synopsis: Non-invasive brain stimulation (NIBS) provides a method for safely perturbing brain activity and has been employed in basic research to test hypotheses concerning brain-behavior relationships with increasing translational applications. Here we introduce a novel NIBS method, which opens a new subthreshold experimental space: kilohertz transcranial magnetic perturbation (kTMP). kTMP is a magnetic induction method that delivers continuous kHz-frequency cortical electric fields (E-fields) which may be amplitude-modulated to potentially mimic electrical activity at endogenous frequencies. In the present study, we show that ten minutes of kTMP targeted over motor cortex (frequency = 3.5 kHz, E-field = 4 V/m) can increase cortical excitability for 2 hours compared to sham.

Microglia Depletion Reduces CD8+ T-cell Infiltration into the Injured Brain in Aged Mice after Traumatic Brain Injury

Veronica Villanueva, Northwestern University
NINDS
Poster 87
veronica.villanueva1@northwestern.edu

Introduction: Traumatic brain injury (TBI) afflicts over 3 million Americans every year. Patients over 65 years of age experience increased mortality and greater long-term neurocognitive morbidity compared to younger adults. CD8+ T-cell infiltration after injury has been related to worse neurocognitive outcomes. Aged microglia release ligands for CD8+ T-cells, allowing for selective recruitment into the aged brain. We hypothesize that depletion of microglia will attenuate accumulation of T-cells post-TBI.
Methods: Young adult (14-weeks N=5) and aged (80-weeks, N=3) male C57BL/6 mice underwent microglia depletion via PLX5622, a colony stimulating factor 1 receptor (CSF1R) inhibitor or were kept on a control diet. Depletion was confirmed with flow cytometry. After depletion, mice underwent TBI via controlled cortical impact vs. sham injury. One-month post-TBI, brains were harvested, and flow cytometry was used to assess resident and infiltrating immune cells.

Results: Treatment with PLX5622 significantly reduced microglia with 95% reduction in young mice and 75% reduction in aged mice. Pre-injury, aged mice demonstrated disproportionate T-cell infiltration within the brain as compared to young adult mice. This pre-injury disparity was not influenced by microglial depletion. Post-injury, T-cell infiltration in aged mice was significantly reduced after microglial depletion as compared to aged, injured mice without depletion (from 2% to 0.5% of live cells, $p = 0.03$). Upon further inspection, the loss of T-cell infiltration was specific to CD8+ T-cells as CD4+ T-cells were unchanged after injury. Conversely, CD4+ T-cells were increased in the young mice after PLX5622 treatment one-month post-TBI (from 0.2% to 0.7% of live cells, $p=0.003$).

Conclusions: We hypothesized that depletion of microglia would reduce the infiltration of T-cells after TBI in aged mice. Our data suggest an age-dependent response to TBI that is induced by microglia. Microglia depletion attenuates this response through reduction in CD8+ T-cells in the aged brain, post-TBI. Previous studies displayed the negative impacts of CD8+ T-cells in the aged brain after TBI. Thus, microglia depletion may be a promising therapeutic in aged TBI subjects. Ongoing studies are focused on gene signature changes and neurocognitive impacts of microglia depletion in TBI.

Scn2a Haploinsufficiency Leads to Absence-type Seizures in a Sex-dependent Manner

Vivianna DeNittis, University of California, San Francisco, Gladstone Institutes
NINDS
Poster 88
vivianna.denittis@gladstone.ucsf.edu

Mutations in the SCN2A gene are known to cause epilepsy and are among the top risk genes for autism spectrum disorder. Children with SCN2A-related disorders are also known to have developmental disabilities, motor and verbal delay, visual impairment, repetitive behavior, and sleep disruption. SCN2A encodes for sodium channel Nav1.2, which is known to express in excitatory neurons. We set out to understand how loss of function of the Scn2a gene affects epileptic phenotypes and their circuit mechanisms in male and female mice.

We found frequent, spontaneous, nonconvulsive epileptic activity in the form of spike-and-wave discharges (SWDs) in the prefrontal, somatosensory, and visual cortices of Scn2a+/– male, but not female, mice through electrocorticographic (ECoG) recordings in chronically implanted freely behaving mice. These SWDs were reduced by treating the mice with 200 mg/kg ethosuximide, a drug commonly used to treat thalamocortical absence-type epilepsy. To determine if female mice also displayed changes in brain excitability, albeit more subtle ones, we challenged implanted mice with a pro-convulsant pentylenetetrazole (PTZ, 20 mg/kg). We analyzed the occurrence of non-convulsive SWDs in response to PTZ and found that Scn2a+/– male, but not female, mice showed an increased SWD risk compared with Scn2a+/+ littermate controls. In addition to SWDs, PTZ caused generalized convulsive tonic-clonic seizures in 60% Scn2a+/– males and 0% Scn2a+/– females.

Since thalamocortical circuit alterations are responsible for absence-type seizures, we next assessed its excitability by performing electrophysiological recordings in acute brain slices. First, we examined the cortical circuit excitability in the Scn2a+/– mice by recording extracellular multi-unit firing evoked by electrical stimulation of layer 5 of the medial prefrontal cortex (mPFC). We observed lower spike frequency responses across the mPFC in Scn2a+/– mice compared to wild-type controls of the same sex. Next, we assessed thalamic circuit excitability by conducting ex vivo slice recordings spanning several thalamic nuclei while electrically stimulating in the internal capsule. We found that male Scn2a+– mice had a greater number of evoked spike frequency in the ventroposterormedial thalamus compared to other thalamic nuclei and compared to wild-type littermate controls.

In conclusion, we found that Scn2a haploinsufficiency causes spontaneous, unprovoked seizures and increases seizure risk in adult mice in a sex-dependent manner. Additionally, we have found that Scn2a haploinsufficiency causes opposite changes in circuit excitability in the mPFC and thalamus. Ongoing studies aim to determine the cellular and circuit mechanisms by which Scn2a haploinsufficiency causes epilepsy.

Usability Testing of the HOPE App Platform: An Immersive Telehealth Solution for Older Adults with Diabetes

Gifty Asante, See Yourself Health
NIA
Poster 89
giftyasante@seeyourselfhealth.com

Authors: Gifty Asante, MPH, Sophia Greisner, BS(c), Barbara A. De La Cruz, MPH, Suzanne E. Mitchell, MD, MS

Background: Type 2 diabetes affects nearly 1 in 3 older adults (aged 65+) in the United States, placing them at risk for unhealthy aging and cognitive decline. During the COVID-19 pandemic, use of telehealth and health technology tools surged. However, older adults remain underrepresented in user-centered technology design. The Healthy Opportunities for Personal Empowerment (HOPE) App Platform by See Yourself Health (SYH) aims to bridge this digital divide. Through HOPE's immersive and avatar-driven platform, SYH delivers experiential and evidence-based diabetes self-management education and support.

Objective: (1) To assemble a Patient Advisory Group (PAG) comprised of middle-aged and older adults and (2) gain in-depth understanding of their experiences, perceptions, and usability of the HOPE platform.

Methods: We recruited PAG members from the greater Louisville, KY area. To qualify, participants had to be aged 45+, be English-speaking, and be diagnosed with type 2 diabetes. They needed to have internet access and some experience with using a cellphone, email, or social media. For usability testing, PAG participants were instructed to follow specific navigation exercises. We observed the exercises, and then conducted key informant interviews and a focus group to characterize their experiences. Platform usability was assessed using the 10-item System Usability Scale (SUS); a benchmark SUS score of 68 was deemed usable. Interviews were transcribed, and an iterative codebook was developed. Three trained coders analyzed the data employing a qualitative thematic approach.

Results: Seven participants comprised the PAG. Mean participant age was 56 years, 57% (4) were female, 86% (6) identified as Black/African American, 71% (5) reported some college education, 57% (4) had <$30,000 annual income, and 71% (5) received SYH devices. Mean SUS score was 80.7, indicating strong usability of the HOPE App Platform. Six key themes emerged from the qualitative analysis, reflecting strengths and recommendations. With respect to technology, participants highlighted (1) avatar selection: more phenotypic avatar choices to closely represent themselves, (2) the onboarding tutorial: individualized support to complement self-guided features, and (3) error-correcting: clear instructions to handle missteps. They also

touted group learning, namely (4) access to actionable education and social learning through (5) storytelling among peers and (6) peer connections.

Conclusion: The HOPE App Platform demonstrated strong usability by middle-aged and older adults as indicated by a high SUS score and insightful qualitative feedback. Key factors for enhanced engagement include avatar identification, ease of usability, and social connections.

Supportive Language Patterns in Stroke Caregiver-Patient Dyads: Initial Observations

FedoraBiney, University of Alabama at Birmingham
NIA
Poster 90
fbiney@uabmc.edu

Background: Language style matching (LSM) is an objective metric of synchrony between communication partners based on the coordinated use of function words (e.g., prepositions, pronouns, etc.). LSM is associated with greater perceived social and emotional support in healthy adults, better relationship quality in older adults, and, in an online support forum for breast cancer survivors, increased self-disclosure. LSM has not been explored in stroke patient-caregiver dyad interactions. The objective of this study was to explore the presence of LSM in stroke patient-caregiver dyad interactions.

Design: Cohort study

Participants: 20 participants (10 stroke patient-caregiver dyads). Eligibility criteria for individuals with stroke: > 3-months post-stroke, ≥ 40 years old; have mild-to-moderate cognitive impairment. Caregiver eligibility criteria: a family or informal (non-paid) caregiver >18 years old who can attend study sessions.

Procedure: Each caregiver-patient dyad engaged in a 10-minute video-recorded interview, discussing the patient's independence in completing functional activities and its impact on the dyad relationship. Patients completed measures of social support. LSM was calculated from transcribed interviews using linguistic processing software (Linguistic Inquiry Word Count [LIWC]).
Measures: LSM (range: 0-1) was calculated from transcribed interviews using linguistic processing software LIWC. LSM scores ≥0.85 indicate high synchronicity in conversation. Social support was assessed using the National Institutes of Health (NIH) Toolbox Emotional Support and Instrumental Support questionnaires. Higher T-scores indicate more perceived support.

Results: Stroke dyads had high synchronicity in discussions about independence and relationship quality (LSM scores: M=0.85, SD=0.07) with most dyads (60%), meeting the threshold for high LSM. Patient-rated social support was within normal limits for both emotional support ratings, M=45.0, (SD=12.2), and instrumental support (M=53.3, SD=7.0).

Conclusions: Stroke caregiver-patient dyads in this sample experienced high synchronicity in a discussion of post-stroke independence and its impact on the dyad relationship. In addition, stroke patients in these dyads reported adequate instrumental and emotional support. Further study is planned with a larger sample and application of statistical methods (e.g., multilevel modeling) to evaluate the potential relationship between LSM and social support in both

caregivers and stroke patients. This information would be valuable for psychotherapists and others who do therapeutic interventions with stroke dyads.

Behavioral Analysis Using DeepLabCut & Keypoint-MoSeq

Mary Cooper, University of Alabama at Birmingham
NIA
Poster 91
mbullock@uab.edu

Traditional behavior methods may only measure a small portion of observable, human-defined behaviors. Previous methods for pose estimation involve implanting physical markers onto key points of interest in order to sequence behavioral movements. Video recording and behavioral sequencing using DeepLabCut (DLC) and Keypoint-MoSeq (KPMS) provide a more naturalistic and automated method of behavior analysis with machine learning for markerless pose estimation. Machine learning for pose estimation using motion sequencing has been used to detect behavioral differences that are occluded from traditional behavior assays. We utilized a machine learning pipeline including DLC in order to extract keypoints and sequence the pose of the animal over the course of the video. Keypoint-MoSeq then takes the data from DLC and clusters similar pose sequences into behaviors called “syllables”. These syllables form the overall syntax of the behavioral phrase. Statistical analysis on data from Keypoint-MoSeq analyzes the usage of each syllable across experimental groups. Here we demonstrate this technique in two mouse models of neurodegenerative disease. The results from these behavior assays compared to traditional behavior reveal that machine learning for behavior may be more sensitive and high-throughput. In conclusion, new machine learning methods should be used to compliment existing traditional behavior assays.

A Study of Racial and Ethnic Differences in Willingness to Participate in Preclinical AD Trials

Edwin Duran, UC Irvine Institute for Memory Impairments and Neurological Disorders
NIA
Poster 92
durane2@uci.edu

Background: Alzheimer's disease (AD) is a progressive neurodegenerative disorder, characterized by cognitive decline and memory loss. To reduce the public health burden of AD, disease-slowing treatments need to be developed through clinical trials. AD disproportionately affects racial and ethnic groups, yet these groups remain underrepresented in AD research. The preclinical AD trial requirements of learning one's biomarker status and enrolling with a study partner may differentially impact trial participation among underrepresented groups.

Methods: Researchers conducted mixed-method interviews in multiple languages to collect attitudes towards biomarker disclosure and attitudes toward the study partner requirement. Inclusion criteria included being between the age of 55-85 and being cognitively unimpaired and no diagnosis of a neurologic or psychiatric disease. Participants were recruited through grassroots, community-based strategies.

Results: A total of 263 participants completed the study with a mean age of 68.6 and 74.1% being female. NH White and NH Black participants were more likely to be US born than Hispanic/Latino and NH Asian participants.

Discussion: Researchers will use data from the parent project to assess nativity differences between foreign and US-born participants in their willingness to enroll into preclinical AD trials and learn their AD biomarker status.

Sex differences in the response to high pulse pressure

Skylyn Ferguson, University of Oregon
NIA
Poster 93
sfergus4@uoregon.edu

Background: Elevated arterial pulse pressure (PP) is associated with cognitive decline and Alzheimer's disease (AD). High PP damages the brain vasculature by causing endothelial cell dysfunction. Stiffer cerebral arteries have an impaired ability to dampen PP, which transmits pulsatility further into the microvasculature, where it can damage brain tissue. At the same time, the APOE4 genotype is associated with cerebrovascular dysfunction. However, it is unknown if elevated PP amplifies this risk. Furthermore, female APOE4 carriers are at a higher risk for developing AD than males. Thus, we hypothesized that female APOE4 mice would be more vulnerable to high PP and have greater cerebral artery stiffness and cognitive impairments compared to male mice.

Methods: In male and female mice homozygous for APOE4 and humanized Aβ1-42 (APOE4/hAβ, n=26, 6 months), we assessed ex vivo endothelium-dependent vasodilation by the dose responses to acetylcholine in isolated posterior cerebral arteries (PCAs) following exposure to static pressure (50 mmHg), low PP (50-75 mmHg), or high PP (37.5-87.5 mmHg). PCA endothelium-independent vasodilation was measured by the response to sodium nitroprusside, and stiffness was measured during the high PP condition. We assessed cognition by using the Morris water maze.

Results: Under static pressure, PCA endothelium-dependent vasodilation was similar between male and female mice ($p=0.13$). In females, PCA endothelium-dependent vasodilation was similar between static and low PP ($p=0.37$), while exposure to high PP resulted in a 38% decline in endothelium-dependent vasodilation ($p=0.004$ vs. static). In contrast, PCA endothelium-dependent vasodilation in male mice was similar between static and PP conditions ($p>0.05$). Endothelium-independent vasodilation did not differ between sexes ($p>0.05$). Female mice also exhibited a higher PCA β-stiffness index than male mice ($p=0.03$). Additionally, during the Morris water maze probe trial, females crossed the platform area significantly fewer times than males ($p=0.048$).

Conclusions: Our data indicate that high PP is detrimental to cerebral artery endothelial function in female, but not male, APOE4/hAβ mice. Additionally, female APOE4/hAβ mice have stiffer cerebral arteries and poorer spatial memory than male APOE4/hAβ mice. Our findings suggest that sex may influence the interactive effect of APOE4 and PP on cerebrovascular and AD-related outcomes.

Impacts of Informant Replacement in Global Industry-Sponsored Alzheimer's Disease Clinical Trials

Mikaela Nishida, University of California, Irvine
NIA
Poster 94
mikaeln@uci.edu

Background: In Alzheimer's disease (AD) clinical trials, participants must enroll with a study partner informant who accompanies them to visits and completes validated instruments. Mid-trial informant replacement (IR) has been found to impact academic trial results. We hypothesized that a similar impact would be observed in industry-sponsored trials.

Methods: We conducted a retrospective analysis of two industry-sponsored AD clinical trials testing semagacestat in mild-to-moderate AD. We assessed the relationship between IR and Alzheimer's Disease Cooperative Study-Activities of Daily Living (ADCS-ADL) score between visits using generalized estimating equations (GEE). The outcomes of interest were mean change in ADCS-ADL between successive visits and the mean absolute change in ADCS-ADL between successive visits, which were used to assess variability. Both models were adjusted for a priori-specified potential confounding variables including participant sex, age, informant type, trial, time, and previous ADCS-ADL measurement. To analyze impacts on a primary outcome measure, we used an ANCOVA model to estimate the association between IR and 76-week change from baseline in ADCS-ADL, where we adjusted for participant sex, age, informant type, trial, and baseline ADCS-ADL measurement. We conducted an F-test to compare the variances of this change.

Results: Among N=2642 randomized participants, 72 (~3%) of participants experienced IR at least once, with a total of 81 occurrences. For visits standardized to be three months apart, we estimated that the difference in the mean between-visit change in ADCS-ADL was approximately -1.41 points (95% CI: -3.52, 0.72; P = 0.194) and the difference in the mean between-visit absolute change was approximately 1.85 points (95% CI: 0.22, 3.49; P = 0.026), comparing participants who experienced IR to similar participants who had stable informants. We did not estimate a statistically significant difference in week-76 change from baseline ADCS-ADL (Est. = -0.98, 95% CI: -6.02, 4.06; P = 0.702) or a significant ratio of variances (Est. = 1.09, 95% CI: 0.65, 2.17; P = 0.700) comparing this measure for participants with IR to those with stable informants.

Conclusions: IR is associated with increased variability in ADCS-ADL measurements between successive visits and should be considered when planning AD clinical trials.

Improving Study Recruitment of Older Adult Patients

J'Heannhehbelle Rosier, University of Chicago
NIA
Poster 95
jnrosier.98@gmail.com

Background: Older adults constitute a crucial, yet underrepresented, demographic in clinical research due to recruitment challenges. The Hospitalist Project is an initiative at the University of Chicago Medicine (UCM) with broad goals of providing descriptive data on inpatients.

Objective: This study aims to enhance the recruitment rates of older adult patients within the Hospitalist Project, which surveys all inpatients at UCM bedsides.

Methods: The study focused on patients aged 75 years and above, divided into two groups based on their medical record numbers. Patients with medical record numbers ending in 0-2 formed the experimental group, while those ending in 3-9 comprised the control group. A lead research coordinator and a specialized team of research assistants were dedicated to the experimental group, concentrating on developing and implementing strategies to effectively engage older patients. Data collection occurred over several months, segmented into three major data collection phases.

Results: The experimental group's dedicated efforts led to notable improvement in recruitment rates during the data collection phases, aided by insights gained from observations within the older adult population. Lapses in the execution of the enhanced recruitment strategies between the phases account for the incongruences in recruitment rate improvement.

Conclusion: This study highlights the critical role of targeted strategies in bolstering the participation of older adults in healthcare research. By customizing recruitment approaches and leveraging insights from dedicated teams, a significant enhancement in recruitment rates was achieved. These results underscore the importance of tailored methodologies to address the challenges of recruiting older adults, thus contributing to more comprehensive research outcomes. Emphasizing such targeted approaches in future studies is essential for ensuring inclusivity and deepening our understanding of healthcare needs among older adult populations.

Exploring Care Transition Experiences of Hispanic Patients with Dementia Following Emergency Department Discharge: A Dyadic Qualitative Study

Jacqueline Sandoval, Yale University
NIA
Poster 96
jacqueline.sandoval@yale.edu

Older patients report fragmented emergency department (ED) care, including insufficient communication with clinicians and inadequate referrals to outpatient care and social services. These challenges are likely even greater for those with cognitive impairment (CI) and their care partners (CPs), especially in non-English speaking populations, where language differences bring additional challenges. This study seeks to fill a gap in the literature by exploring ED discharge care transition experiences for Hispanic patients with dementia. Ten dyads – consisting of a patient with CI or dementia diagnosis and their CP – were enrolled in the ED and completed semi-structured interviews (via video or telephone) one week later, addressing their ED and post-discharge experiences. Interviews investigated participants' experiences in the ED and subsequent care transitions back to the community. Interviews were recorded, transcribed and coded by three research team members for thematic content, adopting a combined deductive-inductive approach until thematic saturation reached across all dyads. Prespecified codes were adapted using the National Quality Forum's Quality Measurement Framework on ED Transitions of Care and included eight outcomes for ED transitions of care: accessibility of services, shared decision-making, connection and alignment, care coordination, information sharing/communication, safety, healthcare utilization/costs, and experience of care. Key study findings emphasize patient and CP priorities of shared decision-making with the ED treating team, how patients and CPs manage language barriers and cognitive impairment challenges, and identifying factors that either support or hinder the quality and safety of ED discharge care and transitions back home.

Faster DunedinPACE, an Epigenetic Clock for Pace of Biological Aging, is Associated with Accelerated Cognitive Aging Among Older Adults in the Framingham Heart Study

Micah Savin, Columbia University
NIA
Poster 97
ms6870@cumc.columbia.edu

Objective: Biomarkers that predict the heterogenous nature and late onset of cognitive decline are needed to: 1) advance research identifying risk and resiliency and 2) evaluate geroscience interventions designed to delay or prevent the progression of Alzheimer's disease and related dementias (ADRD). The DunedinPACE epigenetic clock is designed to measure pace of biological aging, a major risk factor for cognitive decline, and is therefore a promising candidate biomarker. In prior studies, we showed that the DunedinPACE epigenetic clock was predictive of general cognition in mid-life adults and dementia in older adults. Here, we (1) investigate if DunedinPACE is associated with cognitive aging, (2) examine the extent to which these associations are independent of education, and (3) explore whether education modifies DunedinPACE's associations with cognitive aging.

Participants and Methods: We analyzed data from the Framingham Heart Study Offspring cohort. Our analysis sample included participants with neuropsychological testing data and blood DNA methylation data collected within 14 months of their baseline cognitive assessment (n=2,296 non-Hispanic White adults, 46% male; M age = 61.6 ± 9.0 [25-101y]). Comprehensive cognitive assessments were performed annually for up to 12 years (Mdn follow up visits = 3 visits; Mdn visit interval duration = 362 days). The DunedinPACE epigenetic clock was measured from Illumina 450k microarray DNA methylation data (Belsky et al., 2022). Global- and domain-specific cognitive functioning T-scores were calculated according to the methods described in Au et al., (2004) and Downer et al., (2015). Education was measured in years of completed schooling. A series of growth curve models tested the interactive effects of DundeinPACE and education upon baseline and longitudinal changes in global unadjusted T-scores. All models included covariates to adjust for cellular composition of blood samples, smoking status, sex, age at baseline (specified as a quadratic term), and date of blood draw.

Results: A faster DunedinPACE was associated with worse global cognition and steeper decline in cognition over time (Bs=-.37 - -.45; ps< .001). After adjusting for education, DunedinPACE remained robustly associated with global cognition and steeper decline in cognition over time (Bs=-.33 - -38; ps<.01). In effect modification analyses, higher education buffered the effect of faster DunedinPACE upon global cognition at baseline (B=-.21; p<.01), but did not significantly modify the effect of DunedinPACE upon cognitive decline over time (p=.95).

Conclusions: The presented findings support prior work that highlights the role of systemic biological aging in cognitive decline, and further validates the utility of the epigenetic clock,

DunedinPACE, as a potential biomarker for decline in cognitive aging. Further validation of DunedinPACE and its clinical utility as a biomarker for geroscience interventions targeting ADRD is warranted. Greater years of education appears to mitigate some of the deleterious effect of biological aging upon cognition, consistent with the available literature suggesting that education remains an important area of potential intervention. Future studies should critically examine these relationships among nationally representative samples and diverse samples disproportionately impacted by ADRD.

Assessment of the Association of Eicosanoids with Incident Stroke Over Decades in the Atherosclerosis Risk in Communities (ARIC) Study

Alexis Simpkins, Cedars-Sinai Medical Center
NIA
Poster 98
alexis.simpkins@cshs.org

Eicosanoids (EIC) are lipid mediators that play a systemic role in inflammation and, more specifically, contribute to the process of neurovascular coupling in the brain. Though EICs have been associated with immediate stroke risk and stroke risk factors, the long-term risk and associations with stroke risk factors have not been previously studied. Plasma EICs (214) were measured using non-targeted liquid chromatography mass spectrometry in conjunction with chemical networking of spectral fragmentation patterns among participants of the Atherosclerosis Risk in Communities Study at visit 2 (1990-92). Incident stroke (ischemic and hemorrhagic) was ascertained until the end of 2021 with adjudication by an expert panel. Cox regression was used to estimate the hazard ratio (HR) for incident stroke per doubling of EIC levels, and p-values were false discovery rate (FDR)-corrected. Primary model 1 adjusted for age, sex, race/center, and additional models (4 in total) were adjusted for stroke risk factors (eGFR, BMI, hypertension, diabetes, current smoking status, total cholesterol, prevalent atrial fibrillation, prevalent heart failure, prevalent coronary heart disease, aspirin use, cholesterol-lowering medications, anticoagulation medication use, time-dependent incident atrial fibrillation, and incident anticoagulant use). Among the 9,444 participants included, the mean age was 57 (6 SD), and 43% were men. Over a mean of 23 (9 SD) years of follow-up, 950 participants had an incident stroke. In model 1, higher levels of 9 EICs were associated with a higher risk of incident stroke (11t LTD4 [HR 1.21, p=7.4E-05], 5S HpEPE [HR 1.21, p=0.005], LXA5 [HR 1.15 p=0.006], 13 HpODE_a [HR 1.17 p=0.009], 17S HpDHA_a [HR 1.16, p=0.018], 15 oxoEDE_a [HR 1.29 p=0.03], 11, 12 di-HETrE_a [HR 1.21 p=0.03], Arachidonic Acid a [HR 1.17 p=0.03], and 5S HpETE_c [HR 1.18 p=0.04]; and 3 EIC analytes were associated with lower risk of incident stroke (PGF1a_b [HR 0.27 p=0.006], 13, 14 dihydroPGF1a [HR 0.37 p=0.02], 13,14 dihydroPGE1_b [HR 0.5 p=0.03]. Associations did not reach FDR-corrected significance after adjusting for risk factors. Our analysis of this large longitudinal community-based study demonstrates that the risk of incident stroke over decades is associated with alterations in the balance of increasing pro-inflammatory EICs, likely interrelated with the presence of stroke risk factors over time and, interestingly, including an EIC associated with neurovascular coupling. Additional research is needed to investigate which stroke risk factors and stroke subtypes have the strongest associations with plasma EIC levels.

Associations Between Emotion Regulation and Mental Health Among Dementia Caregivers Across Time

Anna Toledo, Georgetown University
NIA
Poster 99
abt50@georgetown.edu

Providing care for an individual with dementia is an emotionally challenging experience that can result in poor mental health, including symptoms of depression and anxiety. Caregivers may be able to protect their mental health by employing emotion regulation strategies, such as cognitive reappraisal (i.e., re-interpreting the meaning of a situation) and expressive suppression (i.e., inhibiting expressions of emotion). The current study investigates whether cognitive reappraisal and expressive suppression predict changes in mental health (i.e., depression and anxiety) among caregivers across a 6-month period. Caregivers (N = 293) completed the Emotion Regulation Questionnaire (ERQ), the Center for Epidemiologic Studies Depression Scale (CES-D), and the Beck Anxiety Inventory (BAI) across three waves of data collection (baseline, three months, six months). A series of longitudinal structural equation models (SEM) within a dynamic panel model approach revealed that (1) reappraisal and suppression remained relatively consistent over time, and (2) overall, caregivers had better mental health if they reported using more reappraisal (β = -0.29, 95% CI [-0.43, -0.15], $p < .001$) and less suppression (β = 0.21, 95%CI [0.09, 0.36], $p = .01$). In addition, (3) more reappraisal, but not suppression, was associated with better mental health over time. These findings suggest that caregivers' use of reappraisal plays a pivotal role in shaping their mental health outcomes over time, offering a potential avenue for intervention and support.

Can’t Get No Satisfaction: Developing a Fly Model of Hedonic Tolerance

Pearl Cummins-Beebee, University of Utah
NIA
Poster 100
pearl.cummins@utah.edu

Substance use disorder (SUD) is the chronic and uncontrolled use of a substance (e.g., alcohol), despite adverse consequences. These negative consequences are key contributors to relapse and are known to drive continued substance use. In 2022, the National Survey on Drug Use and Health reported that 17.3% of the US population aged 12 or older have an SUD, making it apparent that we need to understand the mechanisms of these consequences to help prevent relapse. One of these negative consequences is hedonic tolerance, the reduced reactivity to rewarding stimuli after drug exposure. There is little mechanistic information known about hedonic tolerance, and Drosophila melanogaster provide an avenue to determine neuronal and molecular mechanisms due to their conserved neurotransmitter systems involved in reward and face-valid SUD-like behaviors. Here, we describe a new fly model of hedonic tolerance. We repeatedly exposed flies to ethanol (EtOH), then measured two readouts of hedonic tolerance, feeding initiation (i.e., if the fly chooses to eat a sweet food), and drug preference. First, we used a blue dye feeding assay to measure the feeding initiation (FI) of a non-caloric sweetener, sodium saccharin. Feeding is both calorically driven, where food is eaten for survival, and hedonically driven, where food is eaten for its rewarding value. To understand hedonic tolerance, we need to understand hedonically driven FI, so we used a non-caloric sweetener to control for calorically driven FI. We found that repeated EtOH exposure results in diminished FI of sodium saccharin, suggesting that this sweetener is less rewarding to the fly. Next, we wanted to determine if this finding was generalizable to other rewarding substances, like amphetamine. Previously, our lab determined that flies could develop a preference for amphetamine, similarly to how humans develop a preference to their drug of choice. To measure the development of amphetamine preference, we used the Fly Liquid-food Interaction Counter. We found that repeated EtOH exposure prevents the development of amphetamine preference, suggesting that amphetamine is less rewarding to flies. Both results together diminished FI and the prevention of amphetamine preference, suggesting that our EtOH exposure paradigm is inducing hedonic tolerance in the fly. This novel fly model of hedonic tolerance is a tool that will propel the investigation of the circuitry and molecular mechanisms underlying this behavior.

Assessing the Effects of Prenatal Cannabinoid Consumption on Fetal Brain Vasculature Utilizing Optical Coherence Angiography

Jessica Gutierrez, University of Houston
NIA
Poster 101
jgutie41@cougarnet.uh.edu

Prenatal cannabinoid exposure causes a decrease in cerebral blood flow, leading to neurodevelopmental and morphological alterations in the developing fetus. These include fetal growth restriction, learning disabilities, and memory impairment, among other negative outcomes. There is a fundamental lack of understanding of the severe effects of cannabinoid consumption during pregnancy, especially on vasculature development. Therefore, in this study, we assess the multiple dosing effects of cannabinoid exposure on fetal brain vasculature in utero. We analyzed the effects of different cannabinoid concentrations (0.0625 mg/kg, 0.25 mg/kg, and 1.0 mg/kg) on fetal brain vasculature. We administered the same dose of CP55,940 at gestational days (GD12.5, 13.5, and 14.5) and utilized correlation mapping optical coherence angiography to image changes in fetal brain vasculature. Results show significant vasoconstriction of the main blood vessel for all administered dosages. The difference in the primary blood vessel diameter before and after the final cannabinoid exposure at GD14.5 shows that there was a dramatic difference in the vasculature diameter before the last dose compared to the vasculature when dosed with the vehicle solution. For the lowest dose, 0.0625 mg/kg of CP55,940, there was a greater decrease in the main blood vessel diameter over time. For 1.0 mg/kg of CP55,940, the difference in vessel diameter over time was decreased, but vasoconstriction was noticeably greater when comparing the fetal brain vasculature before the last dose and when dosed with the vehicle. Overall, cannabinoid consumption resulted in a severe decrease in blood flow in the fetal brain.

Addressing Structural Disparities for Children with Early Communication Disorders Diversity Supplement

Joshuaa Allison-Burbank, Johns Hopkins University
NIDCD
Poster 102
jalliso8@jhu.edu

American Indian and Alaska Native (AI/AN) children experience higher rates of communication disorders (CDs) compared to other children in the United States (U.S.). This project includes a large administrative database analysis of the Individuals with Disabilities Education Act (IDEA) Part C early intervention (EI) service use data for AI/AN children in Oregon, Arizona, Indiana, Minnesota, and Florida. This study will assess family, program, and community correlates of structural racism and discrimination at each step of the EI care system, from referral to transition to early childhood special education programs. An explanatory concurrent design with semi-structured interviews of AI/AN families and EI providers serving AI/AN families will be employed to explain and interpret the quantitative data findings, and results will be used to determine strategies for improving EI service delivery to AI/AN children with CDs in the states of interest. Dr. Joshuaa Allison-Burbank's career goal is to become an independent developmental scientist who uses large data to conduct rigorous mixed methods research with AI/AN children with CDs.

The Role of Nonverbal Communication in Autistic Gender-Diverse Adults' Everyday Lives

Maci Brown, Drexel University
NIDCD
Poster 103
bmb392@drexel.edu

Gender diversity is common among autistic people (George & Stokes, 2018a; Walsh et al., 2018), with 25% of the parent project's sample of autistic adults identifying as gender diverse. While the prevalence of gender diversity is well-documented, less attention has been given to how communication differences impact the daily experiences of autistic, gender-diverse individuals. As a core feature of autism (American Psychiatric Association, 2013), communication is closely tied to gender expression and is crucial for self-advocacy in areas like healthcare, especially gender-affirming care (Strang et al., 2021) and mental health (Strang et al., 2023). Despite these connections, research has yet to fully examine how communication strengths and challenges shape everyday life for this population.

Autistic, gender-diverse individuals face compounded challenges, including increased mental health risks and health disparities (Hall et al., 2020; George & Stokes, 2018b). Nonverbal communication barriers, in particular, can impact their ability to navigate essential life domains such as healthcare, employment, education, leisure, and relationships. These barriers often lead to unmet health needs, job instability, social isolation, and diminished quality of life, underscoring the urgent need for personalized, targeted interventions (McConnell & Minshew, 2023; Strang et al, 2020).

This study investigates the role of nonverbal communication barriers in key life situations, considering factors such as gender status, race/ethnicity, age, communication ability (measured by the Communication Checklist Self-Report), and autistic traits (measured by the AQ-10). By exploring how these variables intersect to shape experiences in crucial areas like healthcare, employment, and relationships, this research aims to provide empirical insights that could inform the development of strengths-based, intersectionality-informed interventions. These findings have the potential to promote self-advocacy, improve access to services, foster inclusivity, and guide social and policy changes that enhance the well-being of this historically underserved and marginalized group.

Mitochondrial Dysfunction in the Aging Inner Ear's Cellular Battery

Tyreek Jenkins, Medical University of South Carolina
NIDCD
Poster 104
jenkinst@musc.edu

Background: Age-related hearing loss (ARHL) is a global health concern affecting the communication and livelihood of many older adults. Metabolic presbyacusis, a major type of ARHL, is associated with atrophy of the stria vascularis (SV). The SV, located in the lateral wall of the cochlea, is a vascularized and highly bioenergetic epithelium essential for sound transduction. Specifically, mitochondria-rich marginal cells (MCs) of the SV transport potassium ions to generate the endocochlear potential (EP), which acts as a cellular battery for cochlear hair cells. Increasing evidence supports chronic inflammation of the SV as a key contributory factor of metabolic presbyacusis. Studies show aberrant macrophage activity and inflammation of the SV beginning at middle-age in mice, an age at which there is minimal loss of hair cells and cochlear neurons. However, the underlying mechanisms propagating aberrant macrophage activity and inflammation have yet to be elucidated. Growing evidence signifies mitochondrial dysfunction to be a key contributor to immune cell activation and inflammation. When mitochondria become damaged and/or bioenergetically unfavorable, due to cellular stress, they depolarize and undergo fission to prime damaged mitochondria for autophagy. However, if mitochondrial fission becomes excessive, autophagy can become impaired due to the inability to efficiently form autophagosomes. The present study addressed the hypothesis that mitochondria within strial MCs of aging mice are depolarized and less metabolically active with reduced autophagy compared to young-adult mice, contributing to cochlear inflammation and auditory functional decline.

Methods: The hearing sensitivity of young-adult (2-4 months), middle-aged (15-18 months), and aged (≥ 24 months) CBA/CaJ mice were assessed by measuring the auditory brainstem response (ABR). The SV was then dissected from the cochlea and loaded with tetramethyl rhodamine methyl ester (TMRM) to assess mitochondrial membrane potential via live-cell confocal imaging. In addition, SV explants were excited using two-photon imaging to evaluate NADH autofluorescence (an indicator of mitochondrial metabolic activity). Mitochondrial fission was assessed using quantitative immunohistochemistry of phosphorylated dynamin-related protein 1 at serine 616. To evaluate autophagy, young-adult (2-4 months) and middle-aged (10-14 months) GFP-LC3 transgenic mice were exposed to an octave-band noise (8-16 kHz) at 106 dB SPL for 2 hours to stimulate autophagy. Cochleae were collected 1 day post noise exposure to assess autophagy via LC3 sequestration. Hearing was assessed before and after noise exposure via ABR.

Results: Middle-aged CBA/CaJ mice exhibit reduced hearing sensitivity and mitochondria within strial MCs that are significantly depolarized with increased NADH levels and mitochondrial fission. Furthermore, young-adult GFP-LC3 mice exposed to noise showed

increased LC3 puncta per strial MC, indicating active autophagy. In contrast, middle-aged GFP-LC3 mice showed reduced sequestration of LC3 puncta, suggesting impaired autophagic activity. Improper autophagic activity could negatively affect clearance of damaged/dysfunctional mitochondria, thus contributing to immune cell activation and inflammation.

Conclusion: The understanding of age-related mitochondrial alterations in MCs of the SV will aid in the development of therapeutic agents designed to combat cochlear inflammation via targeting mechanisms aimed at preserving mitochondrial function such as mitochondrial autophagy (i.e., mitophagy).

Does Prosodic Richness Impact Spoken Emotion Identification?

Devon Major, Boys Town National Research Hospital
NIDCD
Poster 105
devon.major@boystown.org

In the auditory domain, emotional information is conveyed through how an individual speaks, known as emotional prosody. Voice pitch contour (f0) is a primary cue for accurately perceiving emotional prosody in normal hearing individuals. In cochlear implant (CI) users, the availability of voice pitch cues within the signal is severely limited, which may serve as a fundamental reason why CI users often perform poorer in accurately identifying spoken emotions.
In the combined auditory-visual domain, such as face-to-face communication, auditory emotional prosody is supplemented by additional visual cues. Upper face movements, such as those involving the eyes and eyebrows, contribute to emotion perception and may compensate for degraded auditory emotional prosody. Even when these visual cues are available to CI users, they sometimes exhibit a deficit in audiovisual integration on emotional perception tasks. One possible explanation is that they may focus more on the speaker's lower face (i.e., lip reading) during face-to-face communication, potentially missing visual emotion cues.
The aim of this study is twofold. First, this study aims to determine if the availability of f0 contour cues within speech affects the accuracy of vocal emotion identification in normal hearing individuals and those who listen through a CI. Secondly, this study aims to test the hypothesis that a CI user’s eye gaze pattern in auditory-visual conditions differs from normal hearing listeners, specifically that CI users look more at the mouth. This presentation will describe where we currently are in experimental design, the pilot data collected and the next steps toward project completion.

Dynamics of Emotion Processing in Post-stroke Aphasia: Insights from Continuous Valence Ratings During Naturalistic Movie-viewing

Manuel Marte, Boston University
NIDCD
Poster 106
mjmarte@bu.edu

This study examines emotional reactivity and language processing in persons with aphasia (PWA) using a naturalistic movie-watching paradigm. We compared 23 PWA (mean age = 60.12, SD = 11.23; WAB-R AQ = 74.13, SD = 15.21) to 37 healthy controls (HC) (mean age = 45.60, SD = 15.21) on continuous valence ratings during movie clips and subsequent language tasks. Time-series analysis revealed a significant Group × Second interaction ($p = 0.0234$) and main effect of Group ($p = 0.0403$), with PWA showing a positivity bias. Multiscale sample entropy analyses indicated less complex emotional responses in PWA, particularly over longer timescales ($p = 0.0285$). Relative to HC, PWA demonstrated significantly lower accuracy on comprehension and antonym generation tasks (both $p < 0.001$). Importantly, in PWA, emotional response complexity positively correlated with comprehension performance ($\beta = 5.0527$, $p < 0.001$). Critically, the complexity of emotional responses itself was moderated by aphasia severity ($\beta = 7.133e\text{-}04$, $p = 0.0029$). These findings suggest that language impairments in aphasia affect emotional processing in naturalistic contexts, potentially due to disrupted predictive processing mechanisms. This approach provides novel insights into language-emotion interactions in aphasia, with implications for assessment and intervention strategies.

The Interaction of Language, Executive Functioning, and Structured Physical Activity for Children with Down Syndrome

Jessica Mattingly, Boys Town National Research Hospital
NIDCD
Poster 107
jessica.mattingly@boystown.org

Purpose: This study's purpose was to compare the differences in amount of physical activity, executive functioning skills, and language abilities between children who are typically developing and children with Down Syndrome. Further, the study aimed to evaluate the relationships between language, executive functioning, and physical activity in children with Down syndrome.

Method: This study included 50 monolingual children between the ages of 7 and 18: 25 children with Down syndrome and 25 children with no biomedical diagnosis. Parents of children in each group completed a report on deficits in executive functioning (the Behavior Rating Inventory of Executive Function-Second Edition) and a questionnaire regarding participation in physical activities; the children participated in performance-based measures of language (the Clinical Evaluation of Language Fundamentals-Fifth Edition) and executive functioning (NIH Toolbox Cognition Battery).

Results: Analyses revealed that children with Down syndrome have significantly lower participation in structured physical activities as well as significantly lower language and executive functioning skills than children with typical development. Executive functioning significantly predicted language outcomes for all children, but especially for the children with Down syndrome. Further, participation in physical activities also predicted language skills; but there was no moderation effect of physical activity participation on the relationship between executive function and language.

Conclusion: This study supports the idea that children develop as dynamic systems, and it represents a first step in identifying how participation in motor activities relates to language and executive functioning development in children with Down syndrome. These findings support multi-domain interventions for language skills in children with Down syndrome.

Identifying the Mechanisms of Astringency Transduction

Mikaéla Murph, New York University College of Dentistry
NIDCD
Poster 108
mcm837@nyu.edu

Astringency is defined as a dry, rough, and puckering sensation that is associated with the consumption of plant-based foods that contain phenolic compounds, namely tannins. Astringency sensation depends on activation of trigeminal neurons, suggesting that transduction depends on somatosensation rather than taste. Chemosensory and mechanical mechanisms of phenolic compound transduction have been proposed, with evidence supporting both. Using a combination of in vitro and in vivo calcium imaging of trigeminal neurons and brief access preference testing in transgenic animals, we aim to identify the cellular and molecular mediators of astringency transduction. Preliminary in vivo calcium imaging has shown that trigeminal mechanosensory neurons that respond to tannic acid are responsive to stroking but not pressure, a response profile that is highly represented by Vglut3 lineage trigeminal neurons. We found that 40% of Vglut3 lineage neurons respond to tannic acid, suggesting that Vglut3 lineage neurons may be involved in chemotransduction of tannic acid. Behavioral assays show that neither Piezo2 knockout in Vglut3 lineage neurons nor Piezo1 knockout in the lingual epithelium affect tannic acid aversion, indicating that aversion is not mediated by mechanotransduction.

Anatomy of Tongue-Innervating Mechanoreceptors

Thomas Myers, University of Louisville
NIDCD
Poster 109
tamyer02@louisville.edu

Somatosensory innervation of the oral cavity enables us to detect the various textures of the foods we consume. To date, little is known about the genetic identity and anatomy of mechanoreceptors innervating the oral cavity. Taste buds within fungiform papillae are surrounded by nerve fibers that express the mechanosensitive channel Piezo2. Fungiform papillae also express neurotrophin-3 (NT-3), so we asked whether neurons innervating fungiform papillae express TrkC, the receptor for NT-3. We found that TrkC+ neurons innervate fungiform papillae and fibers are Piezo2+. We sought out more specific genetic labels by examining Pvalb and VGLUT3 expressing neurons. These neurons have overlapping expression with TrkC, but not with each other. We then compared three genetically identified putative mechanosensitive neuron types: TrkC, Pvalb, and VGLUT3 across postnatal ages. In P120 mice, an average 79% of fungiform papillae are innervated by TrkC+ neurons, 80% by Pvalb+ neurons, and 30% by VGLUT3+ neurons. We found that the number of fungiform papillae innervated by TrkC+ fibers decreased from 100% to 79% by P120. Pvalb+ fibers first innervate fungiform papillae at P30, and the number of innervated papillae increases with age. Interestingly, VGLUT3+ fibers first innervate fungiform papillae at P60. We found that Pvalb+ neurons are NFH+/CGRP-, indicating that the Pvalb+ population consists of A-fibers (NFH+), but not c-fibers (CGRP+). This was corroborated by our finding that Pvalb+ nerve fibers are myelinated. VGLUT3+ neurons consist of two populations: one population that is NFH+ and another that is NFH-. This indicates that VGLUT3+ neurons range from C-fibers to A-fibers. These data provide the anatomical underpinnings for interpretation of future functional experiments.

Psycholinguistic Effects on Silent Reading Comprehension Accuracy in Aphasia-based Alexia

Candace van der Stelt, University of Pittsburgh
NIDCD
Poster 110
cav122@pitt.edu

Authors: Candace M. van der Stelt1, Sarah E. Wallace1, Elizbeth B. Madden2, and Michael Walsh Dickey1,3,4

Affiliations:
1. Communication Science and Disorders, University of Pittsburgh, Pittsburgh, PA
2. Communication Science and Disorders, Florida State University, Tallahassee, FL
3. Veterans Administration Pittsburgh Healthcare System, Pittsburgh, PA
4. Center for the Neural Basis of Cognition, Carnegie Mellon University, Pittsburgh, PA

Introduction: Aphasia-based alexia results from damage to the sublexical-phonological and/or lexical-semantic routes of reading (Rapcsak et al., 2007; Ross et al., 2017). The gold standard for diagnosis is oral reading performance on words of varied frequency, spelling-to-sound consistency (hereafter, "consistency"), and imageability, which differentially rely on these two reading routes (Friedman, 2002). However, alexia manifests in difficulty with both oral and silent reading (Webster et al., 2023). It remains unclear if psycholinguistic effects on silent reading comprehension parallel those observed in oral reading, given that the goal of comprehension is extraction of meaning, rather than verbal production of the word. The aim of the current study is to investigate the impact of word frequency, consistency, and imageability on silent reading comprehension accuracy in a group of individuals with aphasia-based alexia. We hypothesize that imageability, as a measure of semantic processing (Duarte-Expósito et al., 2004), will predict accuracy, particularly for individuals with deficits in the lexical-semantic route.

Methods: Thirty-seven individuals with alexia following a left-hemisphere stroke (Brookshire Madden et al., 2018) completed two silent reading tests from the Psycholinguistic Assessments of Language Processing in Aphasia (PALPA 50 – Written Synonym Judgment and 51 – Word Semantic Association) (Kay et al., 1996), which are balanced between high- and low-imageability items. To obtain an item-level metric for frequency and consistency, all words within each item were averaged (i.e., 2 words and 5 words, respectively) and dichotomized using the median value. Two logistic mixed effects models (LMMs) tested whether these psycholinguistic features predict silent reading accuracy in individuals with alexia. Next, participants were categorized into two groups: 1) phonological alexia – primary sublexical-phonological impairment and 2) non-phonological alexia – additional lexical-semantic impairment. Separate LMMs tested for group by imageability, frequency, and consistency interactions. Helmert coding was implemented to contrast the effect of all dichotomized

variables on silent reading accuracy (high-frequency vs. low-frequency, high-imageability vs. low-imageability, regular vs. irregular).

Results: For all participants, there was a positive main effect of high-imageability on silent reading accuracy on both subtests (OR = 1.20, $p < .001$; OR = 1.09, $p = .02$, respectively). On PALPA 50, there was also a main effect of high-frequency words, significant two-way interactions of frequency-imageability (OR = 0.85, $p = .005$) and frequency-consistency (OR = 0.61, $p = .05$), and a significant three-way interaction of frequency-imageability-consistency (OR = -1.36, $p = .03$). Participants with non-phonological alexia also had reliably lower silent reading accuracy on both subtests (OR=-1.41, p=.002; OR=-0.82, p=.02). On PALPA 50, there was a significant group-imageability interaction (OR=-1.22, p=.003), such that low-imageability items were read with lower comprehension accuracy, and even more so for individuals with non-phonological alexia.

Conclusions: Consistent with our hypothesis, word imageability influenced silent reading comprehension in individuals with aphasia-based alexia, and had an even greater influence in non-phonological alexia (i.e., sublexical-phonological plus lexical-semantic deficits). This is an important addition to the documented impact of Imageability on oral reading in post-stroke alexia (Crisp & Lambon-Ralph, 2006). Our results support further investigation of alexia interventions that target both lexical-semantic and sublexical-phonological skill rehabilitation (Johnson et al., 2017).

Reexamining Taste Cell Lifespan Using in vivo Two-photon Laser Scanning Microscopy

Brittany Walters, University of Louisville School of Medicine
NIDCD
Poster 111
bnwalt01@louisville.edu

Historically, taste cell turnover has been evaluated using fixed tissue preparations to estimate average lifespan for the taste bud cell types. However, a more complete representation of lifespan could be captured by tracking the lifespan of each cell across time. This not only permits measurement of variation in lifespan for individual cells, but also for each stage of taste bud cell differentiation. In this study, our aim was to determine if in vivo two-photon laser scanning microscopy could be used to measure the lifespan of taste bud cells. If so, what frequency of imaging would be necessary to accurately track the same cells across time? We chose to evaluate type II taste bud cells in T1R3GFP mice. It was determined that type II cells could be accurately tracked using in vivo two-photon microscopy with a time between imaging sessions of 48h. Preliminary analysis concludes that the median lifespan of type II cells was 10 days, slightly longer than the prior reported lifespan of 8 days. Previous studies have estimated cell lifespan beginning at cell division, while our analysis begins at differentiation - so early stages are missed, meaning that type II cell lifespans are likely longer than 10 days. Additionally, repeated observation of type II cells reveals a diversity of cell lifespans: the shortest-lived cells remained in the taste bud for 2 days or less and the longest-lived for 32 days or more. Our findings demonstrate the importance of tracking individual cells across time to gain insight into variation within a cell type.

Age- and Sex-Specific Effects of Oxycodone Self-Administration during Gestation on Offspring Reward Motivation

Chantal Aaron, Tufts University
NIDA
Poster 112
chantal.aaron@tufts.edu

Authors: Chantal C. A. Aaron, Fair M. Vassoler, Elizabeth M. Byrnes

The rates of prenatal opioid exposure (POE) in the United States surged by 333% between 1999 to 2014 and are continuing to rise (Conradt et al., 2019; Haight et al., 2018). A significant short-term outcome of POE is neonatal opioid withdrawal syndrome. However, little is known about the long-term neurodevelopmental consequences on the offspring (Conradt et al., 2019). Exposure to opioids and other addictive drugs have been found to enhance the activation of the mesocorticolimbic dopamine pathway (Abu and Roy, 2019) and clinical studies point to a connection between substance use exposure and modified reward behavior (Conroy, 2023; Blom et al., 2011). We hypothesize that POE will increase reward motivation in offspring, and these effects will be dose dependent.
In the current study, we examine the effect of prenatal exposure to oxycodone (OXY) on POE on reward motivation in adolescent and adult male and female offspring. To investigate the impact of POE on offspring outcomes, we employed a voluntary paradigm of OXY intravenous self-administration in female Sprague-Dawley rats, initiated at least 3 weeks prior to gestation and continued daily throughout pregnancy during 6h sessions. Yoked saline (SAL) controls receive IV saline in matched volumes. On postnatal day 1 (PND1), litters were culled and cross-fostered to drug-naïve dams, to eliminate opioid-induced changes in maternal behavior as a confounding factor in any observed offspring effects. As adolescents and adults, OXY and SAL offspring performed sucrose self-administration (SA). At adolescence (PND30), offspring were trained on 5 days of fixed ratio (FR)1, which then was escalated to FR5 training for 3 days, and then finally three days of progressive ratio (PR) to measure motivation. As adults, these same animals performed 3 days of FR1, followed by 2 days of FR5 and finally 3 days of PR.

Preliminary data show that male offspring prenatally exposed to oxycodone showed increase active lever presses during FR1 as both adolescents and in adulthood. This is an ongoing project exploring the link between POE and reward-related behavior in rodents.

Experiences of Substance Use and Medication for Opioid Use Disorder Stigmas in an Underserved, Rural Community

Morgan Anvari, University of Maryland, College Park
NIDA
Poster 113
manvari@umd.edu

Overdose rates related to opioid and stimulant use have steadily risen in underserved, rural U.S. communities for over a decade. Persistent challenges in these communities include access to and retention of medication for opioid use disorder (MOUD) care, further complicated by stigma surrounding substance use (SU) and MOUD. However, little is known about how these stigmas manifest and affect patients' treatment and recovery in rural settings. Peer recovery specialists (PRSs)—individuals with lived experience in SU and recovery—may offer unique resources to overcome these stigma barriers. This qualitative study aimed to understand: 1) how SU and MOUD stigmas manifest in low-resource, rural communities; 2) how these stigmas influence patients' treatment experiences and preferences; and 3) if and how PRS-delivered interventions can ameliorate stigma-related barriers. Semi-structured interviews were conducted with 25 patients and 5 staff members at a mobile treatment unit in an underserved, rural community, and transcripts were analyzed using thematic analysis. The findings demonstrated the pervasive impact of multiple stigmas (e.g., SU, MOUD, racial, and more), enacted by numerous sources (e.g., pharmacists, family, physicians) on substance use treatment initiation and outcomes. These were uniquely influenced by rural living conditions such as the small social environment, limited privacy, and low openness to treatment/help-seeking. Additionally, results indicated that PRS-delivered interventions have the potential to leverage PRSs' shared lived experiences to shift stigmas and improve recovery outcomes. Understanding patient experiences with SU and MOUD stigmas is crucial for developing innovative strategies to reduce stigma and support recovery.

Planned Use of Medication for Opioid Use Disorder Among Adolescents Entering Treatment for Opioid Use Disorder and Trends in the US, 2017-2021

Jesse Boggis, Geisel School of Medicine at Dartmouth
NIDA
Poster 114
jesse.s.boggis.gr@dartmouth.edu

Background: The American Academy of Pediatrics and other professional societies recommend that clinicians treat adolescent opioid use disorder (OUD) with medication for opioid use disorder (MOUD).

Objective: To examine the association between being an adolescent entering treatment for OUD and having planned use of MOUD and trends in this relationship over time.

Methods: We obtained data on first episodes of treatment for OUD (n=607,361) from the Treatment Episode Data Set – Admissions, 2017-2021. We compared the national pooled proportions of adolescents (age 15-17 years) and adults (>18 years) who had planned MOUD using a mixed effects model with a random effect for state. The model accounted for admission year, sex, race, ethnicity, housing status, insurance type, referral source, treatment setting, and state. The Bonferroni method was used to correct for multiple comparisons. A directed-acyclic graph (DAG) was developed to map assumptions about relationships between variables. Prevalence of MOUD receipt for adolescents and adults was estimated for each year.

Results: Our sample included 1,796 adolescents and 605,565 adults. Approximately 6% of adolescents received MOUD compared to 46% of adults. Adolescents entering treatment for OUD were much less likely to have planned use of MOUD compared to adults (AOR: 0.06 [95% CI: 0.05, 0.07], p <.001). The DAG suggests covariates are not likely to introduce statistical bias. MOUD prevalence of planned MOUD has, overall, been slowly increasing for both groups across 5 years, with adult prevalence slightly decreasing in 2019 and 2020.

Conclusion: Planned use of MOUD was markedly low, despite being the gold standard of treatment for OUD. Adolescents received significantly less MOUD than adults, and this relationship has remained relatively constant over time. Findings suggest treatment and policy interventions are warranted to reduce barriers to MOUD receipt, especially for adolescents seeking treatment.

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A Preliminary Investigation of a Community-Based Participatory Research Approach to Recovery Capital Measures for Emerging Adults (Ages 18-25)

Eden Buell, Chestnut Health Systems- Lighthouse Institute
NIDA
Poster 115
ebuell@chestnut.org

Recovery Capital is commonly defined as an individual's resources for achieving and maintaining recovery. According to a 2022 national survey, 27.8% of individuals with substance use disorder (SUD) fell within the emerging adult age range of 18-25. However, current recovery capital measures do not factor in several considerations that are unique to the emerging adult population. To address this, The Justice-Involved and Emerging Adult Population (JEAP) Initiative and the Collaborative Hub for Emerging Adults Recovery Research (CHEARR) deployed a Community-Based Participatory Research (CBPR) approach to developing a measure of the recovery capital specific to this unique age group. CBPR recognizes the unique strengths of community partners, researchers, and stakeholders, bringing these perspectives together throughout the research process to enhance research outcomes.

Purpose: The purpose of this preliminary investigation is to assess the effectiveness of community board members, JEAP, and CHEARR investigators in implementing CBPR.

Methods: To conduct CBPR research, investigators from JEAP and CHEARR held 9 virtual meetings with all three of JEAP's Community boards (3 meetings total) and both of CHEARR's community boards (6 meetings total). Community board members received materials to learn about recovery capital before the meetings and were asked for guidance on creating a new measure of recovery capital for emerging adults. Community board members were compensated for their time. After gathering insights from members and conducting real-time member checking, the guidance from each board was compiled to develop the next steps in the research process.

Findings: The early results of this initial investigation show that community board members and investigators from JEAP and CHEARR effectively worked together on CBPR. They focused on developing a research priority related to recovery capital. They used the equitable and meaningful partnerships established by community members the JEAP Initiative and CHEARR investigators in the early stages of creating a new measure of recovery capital for emerging adults.

Conclusions: It is essential to involve community board members, particularly those with lived expertise, to ensure that research priorities like this will genuinely benefit the community members who need it the most. By establishing partnerships throughout the research process,

community members, investigators, and stakeholders can allocate resources such as funding, time, and commitment more effectively to enhance recovery science.

Limitations: Given the early stage of research on recovery capital measures for emerging adults, it is difficult to fully assess all the outcomes of the CBPR at this time. Additional time and assessment are necessary to determine the efficiency and effectiveness of the CBPR throughout the entire research process.

Future Direction: Engaging community members in research, particularly those with lived experience, throughout the entire research process can improve the entire research process. Future studies should integrate CBPR to enhance research outcomes in research.

Community Social Relations and Their Impact on Black and Latine Peoples' Substance Use Recovery Journey

Mark Costa, Yale School of Medicine
NIDA
Poster 116
mark.costa@yale.edu

Community engagement has become a needed component to advance and build sustainability in implementing evidence-based practices to address opioid use disorder (OUD) in Black and Latinx communities. We can infer that Imani participants generally lack recovery capital or do not operationalize it at treatment initiation. We hypothesize that the Imani Breakthrough project is a source of recovery capital. It allows participants to initiate, resume, or continue their recovery journey by playing various essential roles in engaging participants into care. In this sense, our project aimed to: 1) evaluate the social network of Black and Latine people with alcohol use disorder (AUD) or OUD enrolled in the Imani Breakthrough intervention and its relationship with their hopes, goals, social and cultural values, and recovery capital; 2) utilize Social Network Analysis methodology to construct a social network assessment instrument for Black and Latine people with AUD or OUD, identifying positive and negative social relationships and values and testing the correlation of this developed measure with other measures and outcomes defined in the parent grant; and 3) assess the feasibility, acceptability, safety, and tolerability of social network analysis as a strategy to assess the social network of Black and Latine people with AUD or OUD. Our study focused on each individual and their relationships – egocentric or personal network analysis. Ten individuals from one cohort at each church were enrolled from six target churches (three Black and three Latine churches). Three individual interviews were conducted with each participant (baseline, three months, and six months – at the end of the intervention). Instrument for interviews with quantitative and qualitative questions was developed through a participatory process with members of the community, Imani facilitators, researchers, and members from the advisory board.

Findings: Participants named five people who were helpful with their goals as part of their social network, on average, four of which were family members. Fewer than two people who were not helpful with their goals were named. Most people named could not provide much instrumental, tangible, or housing support; they mostly offered emotional support. Forty percent of participants reported chronic pain that interfered with their lives. Sixty-seven percent of participants who completed the third interview nominated a facilitator as an important person with whom they discussed important matters and who was helpful with their goals. While stopping using and housing were major goals in life at the beginning of the intervention, housing, employment, financial stability, and healthcare were the main goals at the end of the intervention. Participants' social network seems to have increased after the intervention.

Conclusion: Black and Latine people living with AUD or OUD and tremendous social determinants of health have very small social networks, consisting mostly of individuals identified as family members. Pain is a significant unaddressed factor in this population,

particularly related to how it might influence social network types and involvement. Social network improvement seems to be a possible underexplored target to improve the SDOH and engagement with care.

The Moderating Role of Pubertal Development in the Association Between Subjective Socioeconomic Status and Future Career Orientation

Avary Evans, University of Georgia
NIDA
Poster 117
aie92753@uga.edu

Authors: Evans, A. I., Geier, C. F., Oshri, A.

Introduction: Subjective socioeconomic status (SSS) has shown robust associations with many adolescent health and psychological outcomes with a greater predictive value than socioeconomic stats (SES) alone (Ghaed & Gallo, 2007; Operario, Adler, & Williams, 2004). Exploring the association between SSS and career expectations as a proxy for devaluation of long-term goals can elucidate how environmental context manifests in normative adolescent development. Adolescence is characterized by increased reward and sensation seeking behaviors, which have been shown to increase post puberty (Walker et al., 2017). However, few studies have examined how puberty as a developmental stage, in which the adolescent gains independence and becomes more sensitive to environmental influence, may aid or hinder the development of future orientation across ecological contexts.

Methods: This study uses data from the Development of Risk and Resilience Among Rural Youth (DORRY) study. Hypotheses were tested with two waves of data from 121 adolescents (M age = 12.89; 56% female). Pubertal development (PD) and negative career orientation (NCO) were evaluated via youth self-report survey items from the Pubertal Development Scale (PDS) and the YDI Future Orientation Scale (YFD), respectively (Earls et al., 2006; Oshri et al., 2018). SSS was reported via the child's primary caregiver using the MacArthur Scale of Subjective Social Status (Adler et al., 2000).

Results: Direct effects for this analysis showed that SSS had a significant negative association with NCO (β= -.20, p <.05), such that an increase in SSS predicted fewer negative expectations for one's future career. PD showed a significant positive association with NCO (β= .24, p <.05), such that more advanced pubertal development relative to one's peers predicted more negative expectations for one's future career. Moderation analyses showed that PD significantly moderated the association between SSS and NCO (β= -.30, p <.01), such that more advanced pubertal development strengthened the effect of SSS on NCO. Probing via Johnson-Neyman analysis revealed that this interaction was significant for 49.7% of the sample.

Discussion: These results align with the biological sensitivity to context framework, which posits that puberty represents a period of heightened sensitivity to environmental influences (Vijayakumar & Whittle, 2023). The strengthened effect of SSS on NCO during this time underscores the importance of addressing social inequalities early in development. Interventions

targeting self-concept and career guidance during puberty could be particularly effective in mitigating the adverse effects of low SSS on future aspirations.

Characterization of Nicotine Withdrawal Severity Across the Estrous Cycle in Female Rats

Priscilla Giner, The University of Texas at El Paso
NIDA
Poster 118
pginer@utep.edu

During abstinence from chronic nicotine use, the magnitude of withdrawal severity fluctuates across the menstrual cycle in women. Female rodents have a 4-day estrous cycle that can be subdivided into a follicular (estrus and proestrus) and luteal phase (metestrus and diestrus). The follicular phase is characterized by peak increases in estradiol (E2) and progesterone. The luteal phase is characterized by stable and low levels of E2 and progesterone. Our prior work has revealed that the removal of ovarian hormones abolishes the negative affective states produced by withdrawal. Also, the magnitude of withdrawal severity is correlated with high E2 and low progesterone levels. Ongoing mechanistic studies in our laboratory have revealed that the interpeduncular nucleus (IPN) plays a central role in modulating anxiety-like behavior (but not physical signs) of nicotine withdrawal. Previous work in our laboratory has demonstrated that E2 promotes and progesterone reduces anxiety-like behavior produced by nicotine withdrawal in female rats. The goal of the present study was to compare neuronal activation by observable Fos expression in the IPN of nicotine vapor-dependent females that were tested in the follicular or luteal phase of the estrous cycle. Female rats were exposed to 12mg/mL of nicotine vapor for fourteen days. Rats then received administration of the nicotinic receptor antagonist, mecamylamine (3.0 mg/kg), and physical signs and anxiety-like behavior were assessed. Also, vaginal lavage procedures were used to assess the phase of the estrous cycle they were tested in. The rats were then euthanized and brain sections containing the IPN were processed for Fos immunofluorescence to infer the possible IPN subnuclei displaying differential activation. The results revealed an increase in Fos activation in the IPN of female versus male rats. The magnitude of neuronal activation in female rats was correlated with anxiety-like behavior (but not physical signs). The activation of the IPN in males was not correlated with either anxiety-like behavior or physical signs. This work suggests that fluctuations in ovarian hormones alter the magnitude of withdrawal-induced activation of the IPN.

Social Determinants of Health for Predicting Risks of HCV Infection and HCV/HIV Co-infection

Pilar Hernandez Con, University of Florida
NIDA
Poster 119
hernandezcon.mpi@ufl.edu

Authors: Pilar Hernández Con1, MD, MSCE; Debbie L. Wilson1, PhD; Amie Goodin1, PhD; Jingchuan Guo1, MD, PhD; Yonghui Wu2, PhD; Robert Cook3, MD, MPH; Mark Sulkowski4, MD; Haesuk Park1, PhD

Affiliations:
1. Department of Pharmaceutical Outcomes and Policy, University of Florida, Gainesville, FL
2. Department of Health Outcomes and Biomedical Informatics, University of Florida, Gainesville, FL
3. Department of Epidemiology, University of Florida, Gainesville, FL
4. Department of Medicine, Johns Hopkins University, Baltimore, MD

Background: The rapid surge of the opioid crisis has led to an increase in human immunodeficiency virus (HIV) and hepatitis C virus (HCV) outbreaks across the U.S. In 2021, 7% of 36,136 people with a new HIV diagnosis and at least 57% of 5,023 acute cases of HCV were detected among people who inject drugs (PWID). Low rates of infection awareness significantly contribute to the viruses' transmission within these vulnerable populations, increasing morbidity and mortality. Social determinants of health (SDoH) significantly contribute to the HIV and HCV syndemic among PWID by creating unequal distributions of opportunities and resources, which worsen adverse conditions and risky behavioral practices. Implementing comprehensive SDoH screening strategies holds the potential to improve the performance of predictive algorithms aimed at early identification of individuals at risk of HCV infection or HCV/HIV co-infection.

Specific Aims: Aim 1: Develop and validate a polysocial risk score (PsRS) for HCV infection and HCV/HIV co-infection, utilizing natural language processing (NLP). Aim 2: Develop and validate a model utilizing the PsRS to predict HCV infection and HCV/HIV co-infection.

Methods: We will conduct a retrospective study using electronic health record (EHR) data (2016-2023). We will include adults ≥ 18 years visiting any setting of the University of Florida Health (UFH) system who were tested for (1) HCV infection, or (2) HCV and HIV infections. We will identify testing using Current Procedural Terminology (CPT) codes and Logical Observation Identifiers Names and Codes (LOINC). The index date will be defined as the earliest date of HCV or HIV testing recorded during the study period. Once eligible, patients will remain in the cohort until (1) HCV and HIV diagnosis or (2) end of the study period. We will link patient-individual data with publicly available data to construct a PsRS, a distinctive tool

designed to assess the intricate social interactions that influence the HCV/HIV syndemic. SDoH from EHR data will be captured from structured data and from unstructured data using NLP. To construct the PsRS (Aim 1), we will first use and compare two methods for variable selection: (1) criterion-based selection and (2) stepwise selection. We will then use a regression model to develop the PsRS based on the ß coefficients for each SDoH factor. Two distinct multivariable logistic regression models will be developed: (1) a base model, including clinical and demographic variables only, and (2) a full model, including the PsRS in addition to the clinical and demographic variables. We will assess and compare the calibration and discrimination of these two models to assess their predictive performance.

Exploring the Accessibility, Acceptability, and Utilization of a Community-based Harm Reduction Vending Machine Among Persons with Limited Opportunity Structures

Ashleigh Herrera, California State University, Bakersfield
NIDA
Poster 120
aherrera5@csub.edu

The fourth wave of the opioid epidemic has exacerbated health disparities among persons with limited opportunity structures, resulting in significant increases in opioid related morbidity and mortality among Black and Latine communities, as well as people experiencing homelessness (PEH) and justice involved individuals. (1,2,3,4,5) Low-barrier, low-stigma, and low-threshold harm reduction interventions, such as harm reduction vending machines (HRVMs), stand to increase naloxone engagement and re-engagement as well as access to other harm reduction supplies. While several studies have explored the impact of domestic HRVMs on the availability and distribution of harm reduction supplies, including naloxone,(6,7) no known studies have addressed community-based HRVM reach and effectiveness for harm reduction supply access, or acceptability and accessibility among populations with multiple vulnerabilities. To address this issue, we propose to conduct a mixed methods study, including 200 cross-sectional surveys and 20 qualitative interviews with HRVM program participants (50% with past 12-month justice involvement). Together with the parent grant, this will be the first study to explore the accessibility and acceptability of a community based HRVM dispensing naloxone as well as other harm reduction supplies (e.g., sterile syringes, fentanyl test strips, safer injection kits, hygiene kits) among persons with limited opportunity structures. Additionally, it will be the first study to examine the extent to which characteristics of HRVM program participants, such as race, ethnicity, housing status, and history of criminal justice system involvement, affect utilization and dispensation rates of harm reduction supplies, including naloxone, from the HRVM on a longitudinal basis. In addition to the gaps identified above, previous qualitative studies of HRVMs focused on acceptability of HRVMs dispensing sterile syringes or HIV test kits.(13,14,15,16,17) While, internationally, people who use drugs (PWUD) perceived HRVMs dispensing syringes to be highly acceptable,(15,16,17) little is known about the perspectives, experiences, and motivations of how and why people use HRVMs to access naloxone and other harm reduction supplies. Because stigma, structural racism, programmatic barriers, and fear of law enforcement and child welfare services often deter PWUDs from using traditional harm reduction approaches, such as syringe service programs,(18) a qualitative approach will provide much-needed empirical information about accessing harm reduction supplies through HRVMs as compared to traditional harm reduction services. Data collection began on September 4, 2024, and we successfully recruited 9 participants to complete our brief survey.

Diurnal Rhythms in Striatal Acetylcholine and Dopamine Dynamics are Modulated by Differential Cocaine Access

Melody Iacino, Wake Forest University
NIDA
Poster 121
miacino@wakehealth.edu

Despite decades of research into its neurobiological mechanisms, cocaine use disorder (CUD) remains a major worldwide health problem. One variable that is often overlooked in CUD research is cocaine-induced disruption of diurnal (night/day) rhythms. The mesolimbic dopamine (DA) system is an important mediator of motivated and reward-associated behaviors that are maladapted in CUD. Acetylcholine (ACh) from striatal cholinergic interneurons (CINs) modulates mesolimbic DA in the nucleus accumbens (NAc) core via nicotinic ACh receptors (nAChRs) on DA varicosities. Interestingly, mesolimbic DA reciprocally modulates NAc ACh via D2-like receptors (D2Rs) on CINs. Though the effect of cocaine on DA signaling has been extensively studied at single timepoints, cocaine-induced dysregulation of rhythms in NAc DA-ACh interactions and their mechanisms have not been investigated. Here, we used ex vivo fast scan cyclic voltammetry and cell-attached patch-clamp electrophysiology in an adult male Sprague Dawley rat model of cocaine self-administration under various access schedules [(Short continuous access (ShA), long continuous access (LgA), or intermittent access (IntA)] to test the hypothesis that diurnal rhythms in CIN modulation of DA release will vary based on the pattern of cocaine availability. Despite consuming less cocaine than LgA, we show that IntA significantly increased DA release across the light/dark cycle as compared to other groups. Moreover, cocaine intake disrupted rhythms in NAc DA release and D2-autoreceptor (D2AR) sensitivity to dopamine across the light/dark cycle relative to naïve controls. Diurnal variation in D2R sensitivity to dopamine varied by cocaine intake group with IntA and LgA inducing diurnal rhythmicity relative to Naïve and ShA groups. While LgA and ShA disrupted D2AR rhythms, IntA reversed D2AR rhythms in sensitivity to dopamine relative to naïve conditions. Lastly, we show that CINs are more active mid-light versus mid-dark cycle. Ongoing studies are investigating the effects of D2Rs on CIN activity by differential cocaine access. Understanding the influence of diurnal rhythms and cocaine intake pattern on NAc neurochemistry will provide a rationale for targeting receptor systems, like D2Rs on CINs, as a mechanism for restoring rhythms that were present prior to cocaine history.

L-type Calcium Channel Blockade Selectively Attenuates Cue-induced Cocaine-seeking in Female Rats

Violet Kimble, Yale University
NIDA
Poster 122
violet.kimble@yale.edu

Substance use disorders pose a significant public health challenge, influenced by a complex interplay of biological and environmental factors. Notably, gender-specific disparities are evident in substance use disorders, with females often exhibiting heightened susceptibility to drug rewards. To dissect these intricacies, preclinical models of self-administration behavior are employed to model human drug-seeking behaviors. The mesolimbic dopamine (DA) system, and particularly L-type calcium channels (LTCCs) in the ventral tegmental area (VTA) to nucleus accumbens pathway, plays a crucial role in mediating drug-related behaviors. We previously found in male rats that administration of isradipine, an LTCC blocker, attenuates cue-induced cocaine-seeking without impacting natural reward seeking. However, gender-specific effects of LTCC blockade remain relatively unexplored. This study delves into these gender-specific dynamics by investigating the impact of LTCC blockade on cue-induced cocaine-seeking behavior in female Sprague-Dawley rats following cocaine self-administration and forced abstinence. Isradipine effectively diminishes cue-induced cocaine seeking without altering cocaine-taking behavior, demonstrating its potential as a therapeutic target for curbing drug-seeking behavior. Importantly, isradipine does not affect sucrose-seeking or sucrose-taking behaviors, emphasizing its specificity in targeting drug-related processes. The findings in females are consistent with previous experiments in males. These findings underscore the importance of considering gender-specific mechanisms in addiction research and offer insights into developing gender-tailored treatment strategies. Overall, this study sheds light on the intricate interplay between LTCCs and drug-related behaviors, opening avenues for future research and therapeutic interventions in addiction neuroscience.

Characterizing NTSR1-expressing Medial Prefrontal Cortex Afferents into the Nucleus Accumbens in the Context of Opioid-seeking

Crystal Lemchi, University of Minnesota
NIDA
Poster 123
lemch003@umn.edu

There is an urgent need to elucidate the biological mechanisms that mediate opioid use disorder (OUD) and develop interventions to curb the epidemic of opioid overdose deaths. Relapse to opioid use following periods of abstinence is experienced by the majority of patients with OUD and is a risk factor for fatal overdose. Relapse events can be spontaneous or triggered by drug-associated environmental or contextual cues. The neural circuits mediating these events in OUD remain incompletely understood. A growing body of evidence suggests that, like relapse to stimulant seeking, this behavior may be driven by the activity of cortical glutamatergic neurons projecting to the nucleus accumbens (NAc). In rodents, the activation of glutamatergic neurons in the prefrontal cortex (mPFC) that project to the NAc core (NAcC) mediates cue-induced relapse to stimulant seeking. This suggests that targeting these circuits could offer a pathway to developing interventions with limited side effects. However, precise mechanisms through which these circuits influence opioid relapse require further exploration. Though the mechanism is not well understood, the neuropeptide receptor neurotensin receptor 1 (NTSR1) has been implicated in regulating reinstatement of drug-seeking in rodents. NTSR1 preferentially couples to the excitatory Gq family of G proteins, and its ligands have been shown to bidirectionally regulate reinstatement of stimulant seeking; in rodents, NTSR1 agonists induce reinstatement of cocaine seeking while antagonists attenuate cue-induced reinstatement of cocaine seeking. Our preliminary data suggest that an allosteric NTSR1 Gq protein antagonist also reduces cue-induced reinstatement of seeking for the short-acting opioid remifentanil. Using retrograde tracing, we have recently identified a population of mPFC neurons that project to the NAcC and express NTSR1. The structure of this mPFC-NAcCNTSR1 circuit, including its density and neurotransmitter expression, has not been characterized. Moreover, the role of this circuit in controlling relapse to opioid seeking behavior remains unexplored. We hypothesize that this circuit is glutamatergic and that its inhibition will reduce cue-induced reinstatement of opioid seeking. The objectives of this study are to 1) characterize the neurotransmitter profile of the mPFC-NAcCNTSR1 circuit, and 2) explore its ability to regulate cue-induced reinstatement of opioid seeking. We will characterize neurotransmitter profile using RNAscope and manipulate the activity of these neurons in mice with a history of intravenous remifentanil self-administration using chemogenetics. Using an intersectional genetic approach, we will selectively express an inhibitory Designer Receptor Exclusively Activated by Designer Drug (DREADD) in mPFC-NAcCNTSR1 neurons and activate this receptor during cue-induced reinstatement of opioid seeking. Our preliminary results suggest that the majority of mPFC-NAcCNTSR1 neurons are glutamatergic and that an intersectional genetic approach can be used to express an inhibitory DREADD selectivity in mPFC-NAcCNTSR1 neurons. These studies

will reveal the role of NTSR1-expressing mPFC to the NAcC projections in opioid relapse behaviors, potentially identifying these neurons as novel therapeutic targets. This will enable targeted intervention strategies using NTSR1 ligands or neuromodulation to reduce relapse risk in patients with OUD.

Barriers to Mental Health Services in Emerging and Early Adulthood: A 16-Year Longitudinal Study of Youth After Juvenile Detention

Maria Jose Luna, Northwestern University Feinberg School of Medicine
NIDA
Poster 124
marialuna2023@u.northwestern.edu

Background: Over 60% of detained youth have a mental health disorder; more than one third had a disorder 15 years after detainment. Yet, fewer than 20% receive mental health services in adulthood. To improve service utilization, we must identify what barriers prevent justice-involved youth from receiving needed services as they age. In this study, we investigate: (1) the prevalence of barriers to services among emerging and early adults with mental health disorders; and (2) sex, race, ethnicity differences in barriers.

Methods: Data are from the Northwestern Juvenile Project, a 16-year longitudinal study of youth after detention. We recruited a stratified random sample of 1829 youth at a juvenile detention center in Chicago, IL (median age 15 years). We used structured diagnostic interviews to assess mental health disorders 6 and 16 years after detention, when participants were emerging and early adults (median ages 22 and 32 years). We assessed barriers to services among participants with any disorder using the Child and Adolescent Service Assessment and Services Assessment for Children and Adolescents.

Results: Over 80% of males and females were receptive to services during emerging and early adulthood. In emerging adulthood, females had greater odds of experiencing barriers to services than males (45% vs 34%, OR: 1.61; 95% CI: 1.04, 2.50). However, during early adulthood, females had lower odds of experiencing barriers than males (26% vs 40%; OR: 0.52; 95% CI: 0.31, 0.87). The most common barriers among emerging adults were logistical barriers (males, 16.7%; females, 27.9%). In early adulthood, cultural barriers were the most common among males (21.7%) while logistical barriers were the most common among females (14.0%). For the most part, we found few differences in barriers to services by race and ethnicity.

Conclusions: Barriers to services are common among justice-involved youth as they age and vary by sex and race/ethnicity. Findings provide the empirical basis for the development of innovative approaches to improve service use among justice-involved populations.

Effect of Oxytocin on Hyperalgesia in Alcohol-Dependent Rats

John Marendes Jr., University of Tennessee Health Science Center
NIDA
Poster 125
jmarende@uthsc.edu

Introduction: Chronic alcohol exposure in humans and rodents causes tolerance to the analgesic effects of alcohol and enhances pain sensitivity during alcohol withdrawal (i.e., hyperalgesia). The clinical literature suggests a relationship of bidirectional enhancement between chronic alcohol consumption and chronic pain sensitivity (see for review Koob, 2021). Recent work has begun to elucidate the neurobiology involved in this phenomenon (e.g., Avegno, 2018). We previously demonstrated that oxytocin administration reduced alcohol consumption in alcohol-dependent rats (Tunstall et al., 2019). We now hypothesize that oxytocin, known to produce analgesic action in the central nervous system (Petersson, 1996; Poisbeau, 2018; Boll, 2018), could ameliorate hyperalgesia induced by alcohol-dependence. To test this hypothesis, we assessed the ability of central and peripheral oxytocin administration to alter thermal (Hargreaves assay) and mechanical (Von Frey assay) pain sensitivity, in rats made alcohol dependent through repeated cycles of alcohol-vapor exposure.

Methods: Male Wistar rats were surgically prepared with intracerebroventricular (ICV) cannula, tested in the Hargreaves assay, and assigned to matching groups (alcohol nondependent, n = 10; alcohol dependent, n= 8). These groups were monitored via weekly Hargreaves assay to determine alcohol-dependence-induced hyperalgesia. Next, rats were ICV administered oxytocin (0, 0.5, or 5 µg in 2.5 µL saline) prior to Hargreaves testing (Experiment 1) or Von Frey testing (Experiment 2). Finally, rats were intraperitoneally (IP) administered oxytocin (0, 0.1, or 1 mg/kg) prior to Hargreaves testing (Experiment 3) or Von Frey testing (Experiment 4).

Results: Alcohol-dependent rats developed thermal hyperalgesia, observed in the Hargreaves assay (Experiment 1 & 3), however, mechanical hyperalgesia was not observed when the same rats were tested in the Von Frey assay (Experiments 2 & 4). In both the Hargreaves and Von Frey assays, both alcohol-dependent and nondependent rats demonstrated an analgesic effect of ICV or IP administered oxytocin. In cases where dependent rats displayed hyperalgesia, oxytocin treatment was sufficient to return pain sensitivity to the baseline level of nondependent controls. These experiments are now being conducted in female rats.

Conclusion: These data indicate that oxytocin can produce analgesic action in the CNS of alcohol-dependent, hyperalgesic rats. Further, oxytocin signaling may be involved in the neurobiology underlying the interaction of chronic alcohol exposure and chronic pain.

Age-Varying Patterns of Substance Use from Early Adolescence to Young Adulthood Among Latinx Individuals Growing up in Rural or Small-Town Communities in the U.S.

Griselda Martinez, University of Washington
NIDA
Poster 126
gm212@uw.edu

Authors: Griselda Martinez, Brian H. Calhoun, Danielle Pandika, Mariel Sanchez-Rodriguez, Miranda L. M. Delawalla, Martie L. Skinner, Sabrina Oesterle, Katarina Guttmannova

Introduction: Alcohol, cannabis, and cigarette use may begin in adolescence and increase in young adulthood. Though Latinx people in rural communities represent a growing and underserved segment of the U.S. population, patterns of substance use among Latinx youth growing up in rural areas are unknown, representing a critical gap for etiological and prevention work. We examined any past-month alcohol, binge drinking, cannabis, and cigarette use through adolescence and young adulthood in our sample of rural youth, overall and separately, for Latinx children of immigrants (COI; foreign- and U.S.-born children with foreign-born parents), Latinx children of non-immigrants (CONI; U.S.-born children of U.S.-born parents) and non-Latinx White CONI growing up in rural or small-town communities.

Methods: Longitudinal data were from youth who participated in the control arm of a community-randomized trial of the Communities That Care Prevention system (N=1,651; 49.7% female; n=316 Latinx COI; n=154 Latinx CONI; n=916 non-Latinx White CONI) from nine rural or small-town communities in five states. Age-varying patterns of any past-month alcohol use, binge drinking, cannabis use, and cigarette use were examined using logistic time-varying effect models (TVEM). Youth were assessed in grades 6–10 and 12, and at approximately ages 19, 21, 23, and 26.

Results: Ages and prevalences (presented in parentheses) were rounded to one decimal place. Alcohol use prevalence among Latinx COI and CONI increased through around age 16 (0.3) and slowly increased through age 27 (0.6). It increased linearly, peaked at age 24.5 (0.7), and slightly decreased thereafter among non-Latinx White CONI.
Binge drinking prevalence increased through age 27 (0.4), with slower increases after 21 among Latinx COI. For Latinx CONI, binge drinking increased through age 22 (0.4) and oscillated thereafter. Among non-Latinx White CONI it increased and peaked at age 23 (0.4) and decreased thereafter.

Cannabis use prevalence increased up to age 19 (0.2) and remained relatively stable thereafter among Latinx COI. Among Latinx CONI, it increased up to age 18 (0.20) then slowly increased.

Among non-Latinx White CONI it increased and peaked at age 23 (0.2) and remained relatively stable thereafter.
Cigarette use prevalence increased over the course of adolescence, peaked at age 20.5 (0.3), decreased until 25 (0.2), and remained relatively stable thereafter among non-Latinx White CONI. For Latinx CONI, it increased through adolescence, peaked at 21 (0.4), and decreased thereafter. Prevalence of cigarette use was lower among Latinx COI than Latinx COI and non-Latinx White CONI across all ages.

Conclusions: Findings showed that any past-month alcohol, cannabis, and cigarette use tended to increase in adolescence and peak in the early 20s with some distinct patterns across groups. Latinx COI had a lower prevalence of cannabis and cigarette use, and similar prevalence of alcohol use and binge drinking compared to Latinx CONI. Further, the prevalence of substance use tended to decrease at younger ages for non-Latinx White youth, whereas for Latinx CONI and, in some instances for Latinx COI (i.e., any alcohol use and binge drinking), the prevalence remained relatively stable or increased. Future studies should identify risk and protective factors that may explain disparities in substance use in this population.

Self-selected Edible Cannabis Products for Chronic Low Back Pain: Outcomes on Pain, Mood, and Intoxication Effects

Samantha Melendez, University of Colorado Boulder
NIDA
Poster 127
samantha.natal@colorado.edu

Introduction: Nearly two-thirds (62%) of medical cannabis patients in the U.S. and 53% of patients in the U.K. report chronic pain as their reason for using cannabis1,6. Some data suggest that cannabis is effective for improving pain7, yet the research is inconclusive on whether Δ9-tetrahydrocannabinol (THC), cannabidiol (CBD), or a combination of the two (THC+CBD) is the more effective cannabinoid profile for pain management2,5. The primary aim of this study is to evaluate the use of edible cannabis products that are either CBD-dominant, THC-dominant, or have relatively equal ratios of CBD to THC to assess the acute and extended (2-week) effects of these products in participants with chronic, non-specific low back pain.

Methods: The primary pain measure utilized a single item from the Pain Intensity Short Form 3a3 and frequency of use was measured by the Online Timeline Followback assessment (O-TLFB)4. A total of 250 (Female = 141, Male =104) participants with chronic (at least 12 weeks) low back pain who intended to use cannabis products for pain relief were recruited for the study. Participants self-selected and self-administered an edible cannabis product that was categorized as CBD (n =96), THC+CBD (n =118), or THC (n = 36) over a 2-week period. After two weeks of use, participants were reassessed prior to any cannabis use that day to evaluate the extended effects of cannabis on pain-relevant outcomes. At this same visit, measures were taken pre-use, 1-hour, and 2-hours post-cannabis to assess the acute effects. Mixed effects ANOVA models, controlling for age and cannabis pain-relief expectancy, were used to assess the extended and acute effects of cannabis on pain.

Results: Over the 2-week period, there was a significant effect of time on average pain intensity ($p<.001$), indicating an overall reduction in pain for all product groups over extended exposure period. Further, there was a product group x frequency of use interaction, showing that average ($p=.02$) and high ($p=.01$), but not low ($p>.05$), frequencies of CBD product use were associated with significantly lower average pain levels compared to THC+CBD product use at the 2-week reassessment. Finally, there was a significant acute THC dose x time interaction ($p=.019$), with higher THC doses leading to greater pain reduction at both post-use timepoints (1-hour ($p=.008$) and 2-hour ($p=.001$) post-use).

Conclusions: Participants using a higher THC dose at the acute timepoint reported significantly greater decreases in pain intensity, suggesting THC-dominant products can be effective for acute pain relief. More broadly, over the 2-week period all cannabis users experienced significant decreases in pain, with more frequent use of a CBD product showing the strongest effects.

Findings suggest that different cannabinoids may have differential effects for acute versus extended relief from chronic pain.

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Factors Influencing Rapid ART and HIV Care Engagement Among Young Black and Latinx Sexual and Gender Minorities with HIV

Ofole Mgbako, NYU Grossman School of Medicine
NIDA
Poster 128
ofole.mgbako@nyulangone.org

Youth and emerging adults living with HIV (YEA-LWH) who identify as African American/Black or Latinx (AABL) and sexual/gender minorities have the lowest rates of engagement along the HIV care continuum (HCC). The N4 study (R01DA05081) aims to describe HCC trajectories among a group of AABL YEA-LWH (N=270) and understand contextual influences. This NIDA diversity supplement project (the N4-2 study) utilizes mixed methods to examine the role of rapid ART in HIV care engagement and identify other salient factors for AABL YEA-LWH who have been out of regular HIV care.

All N4 study participants were recruited to complete a survey about rapid ART and a subset participated in a one-time, semi-structured in-depth interview. Eligibility criteria include: age 18-28, AABL, NYC or Newark resident, English or Spanish speaking, and HIV positive. Fifty participants were screened, and we conducted 30 in-depth interviews between December 2023 and August 2024. Interviews were transcribed verbatim and translated into English.
Here, we present preliminary findings on important salient factors from the 30 qualitative interviews.

Of 30 participants, the mean (SD) age was 26 (2.7). 53.3% were Black and 40% were Latino. 63.3% were cisgender men, and 26.7% were transgender women or nonbinary. 50% identified as gay, 16.7% bisexual, 16.7% pansexual, 13.3% other, and 3.3% none. Preliminary factors (representative quotes in Figure 1) included: 1) HIV-related stigma, both internalized and interpersonal, negatively impacted the experience being offered rapid ART and staying engaged in care; 2) substance use, often starting at a young age and associated with sex work, had an impact on ability to initiate rapid ART and engage in HIV care; and 3) mental health, often family trauma and life disruption, also impacts rapid ART and ability to stay on the HCC.

Preliminary findings show the critical role substance use, mental health, and stigma play in both the offer and initiation of rapid ART, as well as HIV care engagement for this population. Coding of interview transcripts is ongoing, and a directed content analysis will be conducted to identify major themes. A quantitative analysis examining associations between rapid ART, contextual factors (substance use, mental health and stigma) and HIV care engagement will be conducted. Participants will also participate in focus group discussions using Photovoice methodology.

Cortical Astrocytes Sex-Specifically Modulate EcoHIV-Induced Extinction Learning Impairments

Mark Namba, Drexel University College of Medicine
NIDA
Poster 129
mdn54@drexel.edu

Substance use and human immunodeficiency virus (HIV) remain persistent public health problems throughout the world. People living with HIV (PLWH) use drugs at higher rates than the general population and many studies have demonstrated that addictive drugs can facilitate the pathophysiology of HIV and HIV-associated neurocognitive disorder (HAND), although it remains unclear how HIV impacts reward learning and subsequent addiction-related outcomes. The present study aimed to close this knowledge gap by examining the impact of chemogenetic modulation of cortical astrocytes on extinction learning in a novel rodent model of chronic HIV infection known as EcoHIV. In Experiment 1, male and female C57BL/6J mice (N=48) that were inoculated with EcoHIV (300-500 ng, 0.20 mL, i.p.) or 1X PBS (0.20 mL, i.p.; "sham") were operantly trained to self-administer a 10% sucrose solution beginning on a fixed ratio 1 (FR1) schedule of reinforcement and progressing across test sessions to variable ratio (VR) 2, VR3, and VR5 schedules, where each sucrose reinforcer was paired with a compound light and tone cue. Following self-administration, mice underwent extinction training, where lever presses no longer delivered sucrose or cues. Following extinction training, mice were tested for cue-induced reinstatement of sucrose seeking. After reinstatement testing, mice resumed sucrose self-administration to re-stabilize their sucrose consumption prior to a progressive ratio test. Twenty-four hours after progressive ratio testing, mice were sacrificed via transcaridial perfusion. Fixed brain tissue was sliced and stained for Sox9 and Iba1 immunofluorescence. In Experiment 2, male and female mice (N=40) received intracranial microinfusions of a Gq-DREADD or control (adeno-associated virus) AAV vector into the medial prefrontal cortex (mPFC), driven by a truncated GFAP promoter, prior to EcoHIV- or sham-inoculation. Following recovery, mice were trained to self-administer sucrose as in Experiment 1, followed by 5 days of extinction training, where mice received an injection of deschloroclozapine (DCZ; 0.10 mg/kg, i.p.) 30 mins prior to each extinction session. Mice were then sacrificed 60 mins after the last extinction session via transcardial perfusion for fixed brain tissue collection. In Experiment 1, EcoHIV infection had no effect on the self-administration of sucrose across reinforcement schedules. During extinction training, EcoHIV infection increased active lever presses across test sessions relative to sham mice for both males and females. No significant effect of EcoHIV infection was observed for cue-induced reinstatement of sucrose seeking. Lastly, no effect of EcoHIV infection was observed among male mice for progressive ratio responding for sucrose, while EcoHIV-infected female mice showed significantly lower reinforcers earned. In Experiment 2, sham- and EcoHIV-infected mice that received either AAV vector exhibited no differences in sucrose self-administration akin to Experiment 1. No significant effects of infection or Gq-DREADD stimulation on active lever presses during extinction were observed among male mice. However, among female mice, Gq-DREADD stimulation impaired extinction learning among sham mice, but improved extinction learning among EcoHIV-infected mice. Analyses to quantify mPFC and

nucleus accumbens (NAc) Iba1 and Sox9 expression are ongoing. Taken altogether, our results indicate that EcoHIV infection selectively impairs inhibitory learning among males and females, although the role of cortical astrocytes in regulating this process are sex-specific.

Association between Heightened Vigilance and Cannabis Use Disorder Severity

Emma Quarles, Virginia State University
NIDA
Poster 130
emmaq2019@gmail.com

Introduction: Scant research has explored the relationship between heightened vigilance and cannabis use. Black Americans are a risk demographic for both heightened vigilance and cannabis use. The purpose of the current study was to determine an association between heightened vigilance and cannabis use disorder (CUD) severity in a historically Black college and university (HBCU) undergraduate sample.

Methods: This preliminary sample included 207 self-identifying African American undergraduates (women= 152), with a mean age of approximately 19.78 (SD=1.64) years. Participants were administered a semi-structured interview that included the Mini International Neuropsychiatric Interview, which was used to determine CUD severity. They were also administered a computerized survey that included the Heightened Vigilance Scale, which measures heightened awareness and sensitivity to potentially threatening stimuli.

Results: Thirty (15%) participants met the criteria for severe CUD, twenty (9.7%) participants for moderate, thirty-five (16.9%) for mild, and one hundred twenty-two (58.9%) did not qualify for CUD. Employing a linear regression, results suggested a negative association between Heightened Vigilance scores and CUD severity ($\beta = -0.160$, $p= 0.047$).

Conclusion: Previous studies have found that levels of anxiety can develop into heightened vigilance, which can be positively associated with cannabis use. Future studies should explore anxiety-based underpinnings of heightened vigilance to better tailor cannabis intervention programs for those experiencing increasing levels of vigilance.

Cumulative Lifetime Stress Exposure is Differentially Related to Ambiguity Attitudes in a Clinical Population with Opioid Use Disorder

Joshua Stuckey, Rutgers University
NIDA
Poster 131
js2907@gsbs.rutgers.edu

Human decision-making often occurs in contexts laden with uncertainty. This uncertainty can take at least two forms: decisions in which the probability of an outcome is known (risky) and those in which the probability of an outcome is unknown (ambiguous). Neuroeconomic models capture how these sources of uncertainty impact choice and have revealed human decision makers vary significantly in their risk and ambiguity attitudes. Notably, these attitudes only weakly correlate and have largely dissociable roles in health behavior, including substance use. Recent work has begun to identify factors that help shape how these attitudes might form and are maintained, showing that ambiguity (but not risk) attitudes can be explained, in part, by individual differences in major psychosocial stressor exposure across the lifespan. Here, we sought to examine the generalizability of these findings to a clinical population previously shown to exhibit distinct attitudes toward uncertainty and heightened exposure to psychosocial stress – individuals with opioid use disorder (OUD). Treatment enrolled OUD patients (N = 104, mean age = 49.7) and age- and sex-matched controls (N = 47, mean age = 45.4) completed a comprehensive lifetime stress assessment (the Stress and Adversity Inventory for Adults or STRAIN) and a well-validated economic decision-making task that evaluates both known-risk and ambiguity attitudes. Confirmatory analysis showed that patients exhibited a wide range of risk and ambiguity attitudes and reported a significantly higher number of stressful life events (20-30 more on average) and higher perceived severity of these events (2-3 times more) compared to controls and the original published sample. Interestingly, in patients, greater number and severity of lifetime stressors were selectively correlated with higher ambiguity aversion, but not known-risk aversion. The strength of this correlation did not differ significantly from that observed in controls. Moreover, across all participants, this relationship between stressor number and ambiguity aversion held separately for stressors reported during prenatal development, early life, and adulthood. These findings underscore the potential differential impact of stress across the lifespan on ambiguity attitude within clinical populations. Further, they show that decision-making tendencies in adulthood may be influenced by stressors that occur as early as gestation. This research could offer insights into how environmental and psychosocial stressors shape decision-making in addiction and broader populations.

Replication of Hallucination Severity Associating with Reduced Auditory-language Cortex Connectivity in a Biological Subtype of Psychotic Disorders

Isaac Toscano, University of Chicago
NIDA
Poster 132
itoscano@uchicago.edu

Altered properties of auditory and language brain systems may contribute to auditory hallucinations. Previously, both common and psychosis subgroup-specific functional connectivity associations were found with hallucination severity in the Bipolar Schizophrenia Network on Intermediate Phenotypes-1 (B-SNIP-1) sample (Okuneye et al., 2020). Subgroups included diagnosis (schizophrenia, schizoaffective, bipolar) or the three B-SNIP Biotype groups based on neurobiological similarity. All patients showed increased connectivity within left auditory regions associated with greater hallucination severity. Interhemispheric auditory cortex connectivity was increased for bipolar subjects and decreased for Biotype 1 in association with greater hallucination severity. We sought to replicate these observations.

We used data (n=383) from B-SNIP-2, a replication of B-SNIP-1. From resting state fMRI data, we extracted connectivity from the same clusters of voxels reported in Okuneye et al. to show altered connectivity in association with hallucination severity. We used linear regressions to assess association of connectivity to the Positive and Negative Syndrome Scale (PANSS) hallucination item, as done previously.

Neither the all-patient finding nor the bipolar-specific finding was replicated. Findings of greater hallucination severity in Biotype 1 (N=149) were replicated, associating with reduced connectivity of right auditory association cortex to posterior portions of left auditory cortex ($p=0.028$).

Replicating only the Biotype finding reinforces the potential of this subgrouping approach. Biotype 1 has low auditory processing signal per EEG measurements. Reduced interhemispheric connectivity of auditory cortex may be another manifestation of this group's unique neural pathology. Further work in other brain areas, such as those that regulate auditory cortex, may identify alterations leading to hallucinations in other Biotypes.

Maternal Incarceration and Adolescent Girls' Risk of Substance-exposed Pregnancy, STIs, and HIV

Qianwei Zhao, Baylor University
NIDA
Poster 133
qianwei_zhao@baylor.edu

Research suggests that adolescents with maternal incarceration experiences are more likely to engage in risky sexual behaviors and have sexual health problems than those without maternal incarceration experiences. However, the sexual health risks of adolescent girls and the role of maternal incarceration on their risks remain unknown. This study used the FFCW dataset (N = 1,587) to examine the interrelated risks of substance-exposed pregnancy (SEP), sexually transmitted infections (STIs), and human immunodeficiency virus (HIV) among adolescent girls with maternal incarceration histories and determine the association between exposure to maternal incarceration and these sexual health risks. Bivariate analyses suggested that compared to their counterparts without maternal incarceration experiences, a significantly higher proportion of adolescent girls with such experiences were at risk of SEP (12.24 % vs 2.79 %, $\chi 2 = 13.77$, $p < .001$), STIs (10.45 % vs 3.43 %, $\chi 2 = 8.82$, $p = .003$) and HIV (10.45 % vs 4.23 %, $\chi 2 = 5.78$ %, $p = .016$). Regression analyses revealed that maternal incarceration was associated with significantly higher odds of SEP risk among adolescent girls (OR = 3.94, 95 % CI = 1.37–11.34, $p = .011$). This study suggests the need for sexual health intervention targeting adolescent girls with maternal incarceration histories. Future research on explanatory mechanisms linking maternal incarceration and sexual health risks is necessary to inform services for adolescent girls from extremely fragile families.

Automated Quantifiable Assessments of Sensorimotor Function Using an Instrumented Fragile Object

Michael Adkins, University of Utah
NICHD
Poster 134
michael.adkins@hsc.utah.edu

Accurate assessment of hand dexterity plays a critical role in informing rehabilitation and care of upper-limb hemiparetic stroke patients. Common upper-limb assessments, such as the Box and Blocks Test and Nine Hole Peg Test, primarily evaluate gross motor function in terms of speed. These assessments neglect an individual's ability to finely regulate grip force, which is critical in activities of daily living, such as manipulating fragile objects. Here we present the Electronic Grip Gauge (EGG), an instrumented fragile object that assesses both gross and fine motor function. Embedded with a load cell, accelerometer, and Hall-effect sensor, the EGG measures grip force, acceleration, and relative position (via magnetic fields) in real time. The EGG can emit an audible "break" sound when the applied grip force exceeds a threshold. The number of breaks, transfer duration, and applied forces are automatically logged in real-time. Using the EGG, we evaluated sensorimotor function in implicit grasping and gentle grasping for the non-paretic and paretic hands of 3 hemiparetic stroke patients. For all participants, the paretic hand took longer to transfer the EGG during implicit grasping. For 2 of 3 participants, grip forces were significantly greater for the paretic hand during gentle grasping. Differences in implicit grasping forces were unique to each participant. This work constitutes an important step towards more widespread and quantitative measures of sensorimotor function, which may ultimately lead to improved personalized rehabilitation and better patient outcomes.

Understanding the Associations Between Hand Muscle Motor Evoked Potentials and Motor Function in Stroke Survivors

Jenna Blaschke, Medical University of South Carolina
NICHD
Poster 135
blaschkj@musc.edu

Background: Many stroke survivors experience chronic motor impairments. Of these, more than half suffer from hand impairments. To study the neurological function and recovery of stroke survivors with hand impairments researchers often study the motor evoked potential (MEP), elicited by transcranial magnetic stimulation (TMS), for a single hand muscle. However, multiple upper extremity muscles are utilized to perform activities of daily living, and the extent of impairment differs across multiple muscles for individual stroke survivors. Yet, it has not been investigated whether assessing multiple muscles' MEP could improve prediction of motor recovery. The objective of this research was to determine the role of 3 upper extremity muscles (abductor pollicis brevis, abductor pollicis brevis [APB], first dorsal interosseous, first dorsal interosseous [FDI], and extensor digitorum communis, and extensor digitorum communis [EDC]) MEP in explaining post-stroke hand function.

Methods: Twenty-six stroke survivors participated. Four MEP components were measured: MEP peak-to-peak amplitude, MEP latency, MEP duration, and motor map area using TMS. Motor function was quantified using Wolf Motor Function Test (WMFT) times. Multiple regression analysis was used to investigate the association between WMFT times and APB, FDI, and EDC MEP measures.

Results: WMFT time was explained by MEP amplitude, MEP duration, and motor map area; not by MEP latency. No instances of multicollinearity were detected indicating APB, FDI, and EDC MEP measures are independent. Faster WMFT time was associated with greater EDC MEP amplitude and duration and greater APB motor map area.

Discussion: Motor function was explained by multiple hand muscles' MEP amplitudes, MEP durations, and motor map areas. Consideration of multiple hand muscles provided a comprehensive picture of the hand muscle motor pathways and their complementary association to motor function, post-stroke. Such comprehensive investigation may inform future neurorehabilitation study design and improve prediction models by elucidating the association between multiple hand muscles' MEP measures and function, post-stroke.

VGLL1-mediates Crosstalk of BMP, HIPPO, and WNT Signaling Pathways During Human Trophectoderm Specification

Ruben Calderon, University of California San Diego
NICHD
Poster 136
ricalder@ucsd.edu

The trophectoderm (TE) is the first lineage that is specified during mammalian development and mediates attachment to the maternal endometrium to initiate embryo implantation. The TE gives rise to trophoblasts, the epithelial cells of the placenta that support in-utero development. Embryo implantation is a limiting factor in establishing a successful pregnancy and numerous pregnancy complications are associated with trophoblast dysregulation. Vestigial Like Family Member 1 (VGLL1) is a human-specific transcriptional co-factor that is expressed in the TE of pre-implantation human embryos. Constitutive knockdown of VGLL1 during BMP4-directed differentiation of human embryonic stem cells (hESC) into TE-like cells in vitro indicates it is required for TE lineage commitment, as this results in lower expression of TE lineage markers. Inducible ectopic expression of VGLL1 in hESC upregulates expression of GATA3, an important TE transcription factor. In addition, our comparative analysis of bulk RNAseq data from these models suggests that a subset of placenta-specific genes is regulated by VGLL1-directed transcription, including components of BMP-, HIPPO-, and WNT-signaling pathways that may enable TE-endometrial epithelium communication to initiate embryo implantation. Furthermore, we identified the lysine demethylase KDM6B as a VGLL1-dependent gene during TE-like cell differentiation in vitro. During mouse embryo development, loss of KDM6B affects the removal of repressive histone modification H3K27me3 at TE-specific genes, affects expression of GATA3, and results in blastocyst implantation failure. However, neither the functions of VGLL1 nor KDM6B during human embryo implantation have been reported.

Macrophage Signatures and Dynamics in the Mouse Postpartum Uterus

Maria Natalia Chaves Rivera, Yale University School of Medicine
NICHD
Poster 137
maria.chavesrivera@yale.edu

Authors: M. Natalia Chaves Rivera, Sydney Bell, Abigail Solomon, Aya Tal, Reshef Tal

Affiliation: Department of Obstetrics, Gynecology and Reproductive Sciences, Yale University School of Medicine, New Haven, Connecticut

Background: Macrophages are crucial in uterine physiology, playing important roles in embryo implantation, pregnancy maintenance, and parturition. Macrophages exhibit distinct M1 and M2 activation states; M1-polarized macrophages have pro-inflammatory functions, while M2 macrophages have immunosuppressive and regulatory roles and are involved in tissue repair but also fibrosis in various organs. The postpartum is a period of high susceptibility for intrauterine adhesions in response to injury but the underlying mechanisms are unknown. Macrophages undergo polarization from M1 to M2 profile during pregnancy. While their role in postpartum uterine remodeling is recognized, the dynamics of macrophage polarization profiles during the postpartum period and their relationship to endometrial fibrosis and intrauterine adhesions remain poorly understood. This study aims to establish baseline postpartum changes in uterine macrophages by examining macrophage polarization profiles and dynamics in the postpartum uterus compared to the non-pregnant uterus.

Methods: As a pilot study, uterus and spleen tissues were collected from wild-type C57BL/6J mice at postpartum days (PPD) 1, 3, 7, 14, 21, 28, and from nonpregnant controls (NP). Multicolor flow cytometry was performed with a Fortessa 345A and results were analyzed using FlowJo software to identify leukocyte populations and assess macrophage polarization profiles. Leukocytes were gated as CD45+ and further characterized by CD3+ for T cells and Ly6G+ for granulocytes. Myeloid cells were gated as CD11b+CD3-Ly6G- and further gated on F4/80 to define macrophages (F4/80+). Macrophage polarization within the F4/80+/CD11b+ population was characterized using CD11c and CD86 as M1 markers, and CD206 and CD163 as M2 markers. Data were graphed and analyzed using Prism software with multiple unpaired t-tests corrected for multiple testing using a false discovery rate, reporting significance with $p<0.05$.

Results: At the immediate postpartum (PPD 1), the granulocyte (Ly6G+) population peaked, and macrophage (F4/80+) numbers were significantly higher compared to NP and other PP time points, with a predominance of CD206+ M2 macrophages. The percentage of CD206+ cells at PPD 1 was 43%, significantly higher than in NP (2%, $p<0.0001$) and at subsequent time points: PPD 3 (1.8%, $p<0.001$), PPD 7 (0.92%, $p<0.001$), PPD 14 (0.92%, $p<0.001$), PPD 21 (11.7%, $p<0.01$), and PPD 28 (7.2%, $p<0.001$). This was followed by a rapid shift towards the M1 population (CD86+) from PPD 3 to PPD 14. Specifically compared to PPD 1 (11.9%), CD86

expression was 58.8% at NP ($p<0.001$), 63.6% at PPD 3 ($p<0.001$), 66.9% at PPD 7 ($p<0.0001$), 73.5% at PPD 14 ($p<0.0001$), 38.8% at PPD21 ($p<0.05$), and 42% at PPD28 ($p<0.05$). Interestingly, there was a trend of increased CD206+ M2 macrophage expression at PPD 21 (11.7%) and PPD 28 (7.2%) compared to NP, PPD 3, PPD 7, and PPD 14. Additionally, we observed a significant population of M1/M2 macrophages co-expressing CD86+CD206+ at PPD 1 (37.2%) which was increased compared to NP (7.1%, $p<0.001$), PPD 7 (13.3%, $p<0.01$), and PPD 14 (14.5%, $p<0.05$), with a similar increase noted at PPD 21 (37.2%, $p<0.05$) and PPD 28 (40.4%, $p<0.05$).

Conclusions: The peak in granulocytes (Ly6G+) at PPD 1 is consistent with an acute pro-inflammatory response associated with parturition. The predominant presence of the M2 macrophage population (CD206+) at PPD 1, followed by a rapid shift towards the M1 population (CD86+) from PPD 3 to PPD 14, indicates a dynamic inflammatory response during the early postpartum period. The similarities in the M2 macrophage profiles observed at PPD 1, PPD 21, and PPD 28, along with the coexistence of macrophages expressing both M1 and M2 markers at these time points, underscore the complexity of macrophage polarization during postpartum uterine remodeling, highlighting potential areas for further investigation. These findings offer valuable insights into macrophage polarization profiles throughout the postpartum period. However, to fully understand the role of specific macrophage profiles in fibrosis development and intrauterine adhesions, additional functional studies are needed to better elucidate the implications of these macrophage subtypes for our hypothesis.

Assessing the Perinatal Outcomes and Needs of Women on Probation

Allison Crawford, University of Texas Health at San Antonio
NICHD
Poster 138
crawfordad@uthscsa.edu

Background: Despite probation being the most prominent form of legal oversight for women of childbearing age, this population remains understudied, and assessing their needs is difficult since probation departments nationwide do not systematically track perinatal outcomes. Women on probation have similar inequities as women in prison. However, they also have high rates of violence, which may influence their health. Consequently, there is an increasing need to address perinatal health issues for women on probation.

Methods: We conducted a mixed methods study to assess the perinatal needs of women on community supervision.

Results: We obtained data from 60 women and 13 stakeholders. There are high rates of induced labor, preterm birth, and bleeding disorders. Mood disorder and violence were high before, during, and after pregnancy. The barriers described by the sample associated with probation were costs, time, limited time off, and employment limitations. There is no programming, policies, and protocols, nor tracking of outcomes specific for people who are pregnant, birthing, and postpartum on community supervision; accommodations are given on case-by-case bases and left up to the discretion of the officer.

Conclusion: There is no programming in Texas that focuses on the perinatal health of women on community supervision. Future studies that include mechanisms to enhance social support and self-efficacy with programming to include special accommodations for women during pregnancy, childbirth, and postpartum while on community supervision may enhance outcomes.

Acetaminophen-Induced Toxicity in Lung Epithelial Cells is Cyp2e1 Dependent

Lily Emmanuel, University of Colorado Anschutz Medical Campus
NICHD
Poster 139
lily.emmanuel@ucdenver.edu

Background: Early life acetaminophen (APAP) exposures are thought to be safe due to a lack of observed hepatic toxicity. Hepatic expression of Cyp2e1, the enzyme that converts APAP to toxic metabolites, does not reach adult levels until three months of age. In contrast, clinical studies link early life APAP exposures to long-term pulmonary morbidity, but a known mechanism is lacking. The e18 and P14 developing murine lung expresses Cyp2e1 at levels that exceed adult levels, but whether this increases sensitivity to APAP exposures is unknown. Whether the developing lung and/or specific lung cells are susceptible to Cyp2e1-dependent, APAP-induced toxicity is unknown.

Methods: MLE-12 cells, an immortalized lung epithelial cell line, were evaluated for Cyp2e1 expression using RT-qPCR. As Cyp2e1 expression is beta-catenin dependent, we assessed whether inducing beta-catenin activity through pharmacologic inhibition of GSK3b with LiCl (10/20 mM) could increase Cyp2e1 expression. Cells with and without beta-catenin induction were exposed to APAP at increasing doses (.5/1/5 mM) and evaluated for a pro-inflammatory, antioxidant and apoptotic response, previously demonstrated to play a role in APAP-induced cellular toxicity.

Results: MLE-12 cells expressed Cyp2e1, and expression significantly increased with induction of beta-catenin activity following GSK3b inhibition. APAP exposures caused a dose-dependent increase in Cyp2e1, Mmp9, and the pro-apoptotic Pmaip1 (Noxa). At lower exposures, expression of antioxidant Hmox anti-apoptotic Il6, Bclxl, and Birc5 increased, and this response was blunted at higher exposures. Cells with higher expression of Cyp2e1 demonstrated greater increases in Mmp9, Pmaip1 and blunted anti-apoptotic Bclxl and Birc5.

Conclusion: The MLE-12 immortalized lung epithelial cell line expressed Cyp2e1, and levels increased with induction of beta-catenin activity. At lower levels of APAP exposures, cells responded by upregulating antiapoptotic gene expression, while higher exposures increased pro-apoptotic expression. These results demonstrate that lung epithelial cells may be sensitive to APAP dependent on Cyp2e1 expression and APAP dose. More work is necessary to mechanistically link APAP exposure, Cyp2e1 expression, and lung epithelial cell toxicity.

A Prostate Specific Antigen (PSA) Inhibitor Shows Potential for a Non-hormonal Contraceptive Method

Jeffery Erickson, University of Missouri
NICHD
Poster 140
jeffery.erickson@missouri.edu

Semen liquefaction is a post-ejaculatory process that depends on the enzyme activity of prostate-specific antigen (PSA) to liquefy semen coagulum. This process ultimately facilitates successful sperm motility for fertilization in the female reproductive tract. After reviewing literature on specific PSA inhibitors, we identified three distinct structures, comprising of two triazole inhibitors (B1 & B3), β-lactam analog (β-L), and peptidyl boronic acid (PBA). Thus, we hypothesized that these novel PSA inhibitors have potential use as a non-hormonal contraceptive by disrupting semen liquefaction, ultimately preventing sperm from reaching the site of fertilization. Using in vitro PSA enzyme assays, B1 and PBA were more potent at inhibiting PSA activity than B3 and β-L. B1 was selected as the prototype compound for further studies due to its drug-like property. In silico modeling using AutoDock Vina showed that B1 docks within PSA's active site. Using human semen liquefaction analysis (n=6 healthy donors/treatment), B1 (100μM) was 10x more effective at blocking liquefaction in comparison to AEBSF, a non-specific protease inhibitor control. Using in vitro MTT cellular viability assays, 100μM B1 significantly reduced cellular viability in human vaginal cells to ~60% compared to 100% DMSO control. However, B1 showed no effect on cell viability in human ectocervical or 3D EpiVaginalTM culture. Nonoxynol 9 (N9; spermicide) was used as a positive control, resulting in 0% cell viability. To determine in vivo cytotoxicity, female mice (n=6/treatment) were transvaginally treated with DMSO control, 250μM B1, Gynol (spermicide) or untreated control for 10 minutes. Then, YOYO-1 dye incorporation was measured via immunofluorescent analysis using ImageJ. B1 showed a similar level of cell death compared to DMSO. However, Gynol caused a greater increase in vaginal cell death. Altogether, these studies highlight triazole B1's potential as a prototype for contraceptive development by blocking semen liquefaction, with less cytotoxic effects in comparison to spermicides.

Home Task Practices Increase Stroke Survivors' Real-World Upper Limb Use as Measured by Wearable Accelerometer

Ja'Quann Gallant, Medical University of South Carolina
NICHD
Poster 141
gallantj@musc.edu

Introduction: Stroke is a leading cause of long-term disability, affecting 89 million people globally. Nearly two thirds of stroke survivors have upper limb impairment. Upper limb impairment decreases individuals' independence and ability to participate in meaningful activities in life. Extensive task-oriented rehabilitation therapy has been shown to improve stroke survivors' upper limb movement capacity in the clinic. However, this does not translate to enhanced use of the paretic upper limb in the home. This gap between the clinic and the home may be addressed by home exercise programs that prescribe patients with task practices to be performed at home. However, adherence to home exercises can be low, which diminishes potential benefits. The objective of this research was to determine if the adherence level to home task practices affects the extent of the paretic upper limb use in the community setting.

Methods: Twenty-nine stroke survivors participated in the study (19 males and 10 females, age mean + standard deviation = 58 + 10 years, >6 months post stroke). They had moderate upper limb impairment, as indicated by the upper extremity Fugl-Meyer Assessment score of 36 + 8. All participants received 18 sessions of task practice therapy in the laboratory, administered by a research occupational/physical therapist over 6 weeks. They were also instructed to perform task practices at home, consisting of 4 functional tasks with 75 repetitions each. Participants recorded the number of repetitions of home task practices in a daily log.
Participants wore a 3-axial accelerometer on their paretic wrist before and after the intervention for 3 days each. The average duration per day during which the paretic upper limb movement was detected was quantified. The relationship between the total home task practice repetitions and change in the paretic upper limb use duration in the community was examined using regression analysis.

Results: Participants who completed more repetitions of home task practices had a greater increase in their paretic upper limb use ($p=0.007$). This finding was despite the fact that all participants received the same in-clinic therapy.

Discussion & Conclusion: This research highlights how patient adherence to home exercises plays a significant role in improving the paretic upper limb use in daily living. Future research may investigate personalization of home exercise programs with wearable sensors to enhance patient adherence and outcomes.

Development of Acoustic Startle Response and Prepulse Inhibition in Fragile X Syndrome Mice

Andrea Gensky, Oklahoma State University
NICHD
Poster 142
agripe@okstate.edu

Autism spectrum disorder (ASD) is a neurodevelopmental disability, affecting how a person communicates and interacts with others and their environment. A large part of communicating effectively is being able to accurately and acutely process and localize sounds. The most common monogenic cause of ASD is Fragile X Syndrome (FXS), which is caused by a mutation of the Fmr1 gene that encodes Fragile X Ribonucleoprotein (FMRP). Auditory dysfunction is thought to be caused by an imbalance of excitatory and inhibitory neurological imbalances in the auditory brainstem, where FMRP is highly expressed. We aim to better understand the development of auditory processing in our knock-out (KO) (FXS) and wild-type (WT) mice at different critical time points: P8, P14, P18, P21, and adulthood (85-90 days old), where P is denoted as postnatal followed by how many days old. To measure auditory development, we will be using acoustic startle response (ASR) and prepulse inhibition (PPI) measurements, where ASRs measure whole-body responses to a startle stimulus and PPI precedes the ASR with a certain cue (prepulse), that inhibits the ASR. Therefore, PPI is a measurement of sensorimotor gating, and having improved or diminished responses to startle stimuli will ultimately show whether the animal has any disruptions in the auditory pathway. Additionally, comparisons between KO and WT mice will be analyzed and provide insight into different processing mechanisms.

Impact of PBDE-47 Exposure on Placental Immune Tolerance Mediated by Extracellular Vesicle miRNA-519c

Rahanna Khan, New York University Grossman School of Medicine
NICHD
Poster 143
rahanna.khan@nyulangone.org

Extracellular vesicles (EVs) are stable, membrane-bound carriers of bioactive molecules, such as miRNA. In human placenta, the EV-miRNA 519c is secreted in response to inflammatory stimuli. By suppressing TNF-a production upon repeat inflammatory challenge, miR-519c facilitates immune tolerance, a key process healthy term pregnancy. PBDE-47 is an environmental toxicant with known contributions to preterm birth and disrupted EV-miRNA signaling. Though it was discontinued in 2009, PBDE-47 is a persistent flame retardant with a lasting presence in many older homes. The purpose of this study is to determine whether PBDE-induced changes to placental EV-miRNA may alter placental immune tolerance and promote an inflammatory microenvironment. Full-term human placentas were cultured ex-vivo with exposure to PBDE-47 and repeat doses of LPS to simulate endotoxin challenge. Culture media was collected for EV isolation and inflammatory marker ELISA. Results indicate that treatments are successful in driving an immune tolerance response with a spike in miR-519c upon repeat LPS challenge. A subset of placentas exposed to PBDE-47 lose their immune tolerance and have lower miR-519c production following double LPS challenge. Though more samples are needed to confirm this effect, these data support the multiple hit hypothesis, wherein certain mothers are at higher risk for preterm delivery due to compounding factors such as toxicant exposure, chronic conditions, and maternal stress.

Closing the Gaps: Racial and Ethnic Disparities in Traumatic Childbirth and Co-Morbid Conditions

Kelimer Lebron-Sagardia, Massachusetts General Hospital & Harvard Medical School
NICHD
Poster 144
klebron-sagardia@mgh.harvard.edu

Background: Underrepresented and minoritized women, particularly Black and Hispanic women, face elevated risks of maternal morbidity and mortality in the U.S. However, disparities in maternal mental health remain understudied.

Methods: We conducted surveys across three studies involving Black, Hispanic, and White women. The MGH-Harvard Childbirth Study followed 1,000 women from 32 weeks of pregnancy through postpartum assessments at 1 day, 10 days, and 2, 3, 6, and 12 months. The MGH-Maternal Wellness Study tracked 1,298 women from 32 weeks of pregnancy to 45 days postpartum. The COVID-19 Study included 472 women surveyed from 2 months postpartum who gave birth during the pandemic. Independent Sample t-tests, structural equation modeling, and odds ratios were employed to assess various mental health outcomes during and after pregnancy, focusing on the likelihood of acute traumatic responses to childbirth across racial and ethnic groups.

Results: Minoritized women exhibited a higher burden of maternal psychopathology. Disparities extended beyond postpartum depression, with elevated rates of anxiety, somatization, and acute traumatic responses to childbirth in Black and Hispanic women. Importantly, these disparities were not explained by socio-demographic factors or objective childbirth characteristics, suggesting that racial discrimination may play a role in driving adverse mental health outcomes.

Discussion: This study highlights significant racial and ethnic disparities in maternal mental health. Given the severe implications of maternal psychopathology on both mothers and their offspring, there is an urgent need to address these disparities and support vulnerable populations to improve maternal mental health outcomes.

Characterizing Non-PRC2 Catalyzed Histone H3K27me3 in Transcriptional Regulation

Itzaira Mercado Hernandez, University of Michigan
NICHD
Poster 145
itzaira@umich.edu

DNA and histones in chromatin can be reversibly chemically modified. These chemical modifications are often associated with distinct transcriptional states. Among the most widely studied chromatin mark is the tri-methylation of lysine 27 of histone H3 (H3K27me3). H3K27me3 is associated with silenced states of transcription and is believed to be catalyzed solely by the Polycomb Repressive Complex 2 (PRC2). PRC2 methyltransferase activity requires the presence of its core subunits: SUZ12, EED, and the catalytic subunit EZH2 or EZH1. PRC2 core subunits are essential for mouse embryonic development and their functions in gene regulation have been studied extensively in cultured stem cells. In our studies of mouse extra-embryonic endoderm (XEN) stem cell lines devoid of the PRC2 core subunit EED (Eed-/-) or the PRC2 methyltransferases EZH2 and EZH1 (Ezh2-/-; Ezh1-/-), we unexpectedly found significant levels of H3K27me3 by both western blot and mass spectrometry (MS). Intriguingly, the replication-independent histone H3 variant, H3.3, displayed almost complete retention of K27me3 in PRC2-null Eed-/- and Ezh2-/-;Ezh1-/- XEN cells. In addition, by RNA-seq we observed minimal gene expression changes in Eed-/- XEN cells as compared to Eedfl/- XEN cells. Based on these data, my work tests the hypothesis that non-PRC2 catalyzed H3K27me3 can continue to repress expression of PRC2 target genes in the absence of PRC2.

Glenohumeral Joint Macrostructural Changes Following Brachial Plexus Birth Injury (BPBI)

Vivian Mota, North Carolina State University
NICHD
Poster 146
vmmota@ncsu.edu

Brachial plexus birth injury (BPBI) is a common neonatal neuromuscular injury resulting in muscle paralysis, shoulder contracture, and lifelong arm impairments. Previous studies have shown that altered limb loading due to BPBI can directly affect glenoid formation and growth. However, there is minimal understanding surrounding the timeline for bone deformity development. This research focused on characterizing the glenoid shape changes in Sprague Dawley rat pups who underwent neurectomy surgery 3-6 days postnatally. Our results show the development of glenohumeral deformity at 4 weeks through differences in glenoid inclination angle, glenoid curvature diameter, and humeral head width measurements. This work provides insights into BPBI deformity progression and will help inform optimal timing for clinical interventions to prevent progression of the deformity.

Electromyographic Volitional Control of a Powered Knee Prosthesis for Varied Ambulation Tasks

Rosemarie Murray, University of Utah
NICHD
Poster 147
rosemarie.murray@utah.edu

Most people with transfemoral amputations use passive knee prostheses. These prostheses cannot replace the energy generated by a biological leg, which can make it difficult to perform everyday tasks such as sit-to-stand motions and stair climbing. Powered prostheses can generate positive power and have the potential to make these tasks easier for users. However, in order to be used in daily life, they must be able to coordinate with the user's movement. Current powered prosthesis controllers rely on mechanical sensors which provide users with limited agency over their prosthesis. However, since they are based on the movement of the residual limb, they enforce a specific coordination between the hip and the knee. Certain tasks, such as step-over-step stair ascent, can require particularly difficult coordination patterns that create a barrier to adoption for users. Even for very high-functioning users, this approach fundamentally limits agency over the prosthesis by preventing variation in hip-knee coordination that would allow users to subtly vary the way they perform a task or transition between tasks.

In contrast, electromyography (EMG) offers the potential for increased agency by allowing amputees to control their prosthetic knee in the same way they would a biological leg: through the muscles of their thigh. Here, we show that individuals with transfemoral amputation can voluntarily control a powered knee prosthesis using two electromyography sensors to perform a varied range of ambulation tasks. The proposed controller continuously modulates knee flexion and extension torque based on the EMG signals from the biceps femoris and vastus lateralis of the user's residual limb, as well as the residual thigh angle, prosthesis knee angle, and the ground reaction force. This controller enabled subjects to walk and climb stairs at varied speeds, cadences, and loading conditions. It also enabled users to transition seamlessly through sit-to-stand, walking, stair ascent, and stair descent. The controller offers users a high degree of agency over their prosthesis, which they can use to smoothly transition through a range of ambulation tasks and achieve nuanced variation within specific tasks.

Matrix Metallopeptidase 9 Promotes Human Uterine Contraction

Lauren Parker, University of Nevada, Reno
NICHD
Poster 148
lparker@unr.edu

Authors: Craig Ulrich, Lauren Parker, Janet Lambert, and Heather Burkin

Affiliation: University of Nevada, Reno School of Medicine

Introduction: Matrix metallopeptidase 9 (MMP9) is elevated in human uterine myometrial tissues from preterm laboring patients. We hypothesized MMP9 would enhance both spontaneous and oxytocin-induced uterine contraction in human myometrial tissue and that specific MMP9 inhibition would suppress uterine contraction.

Methods: Uterine tissue was procured from pregnant patients undergoing caesarean section with approval from the University of Nevada Institutional Review Board. Myometrial tissue strips measuring 10x1x1 mm were dissected and placed in baths containing Krebs buffer, maintained at 37°C with a gas mixture of 95% O2 and 5% CO2. Isometric tension changes were monitored using a force transducer. The tissue strips were preconditioned at a basal tension of 2-3 g for at least 30 minutes, exposed to 60 mM KCl for 3 minutes, and then rinsed with Krebs buffer. Upon the onset of spontaneous contractions, the tissue strips were stimulated with 6 IU/mL oxytocin for 20 minutes, followed by the addition of activated recombinant human MMP9 at a concentration of 10 nM or vehicle control. In a subsequent set of experiments, after the development of spontaneous contractions, either 1 μM AG-L-66085 or vehicle control was added as described earlier. In the final series of experiments, contraction parameters following the addition of AG-L-66085 were compared to the baseline of spontaneous contractions. Contraction amplitude, interval, and area under the curve were calculated using LabChart 8 software. The data were normalized to the mean of the baseline and expressed as a ratio (treatment: mean baseline). Statistical analyses were conducted using Graphpad Prism version 10.0.1.

Results: We observed an 18% increase in the oxytocin-induced contractile response, as measured by area under the curve over time in myometrial tissue treated with MMP9 compared to a 12% reduction in vehicle-treated controls ($p<0.001$). This effect was primarily due to an increase in contraction frequency in MMP9-treated tissues compared to controls ($p<0.0001$). Conversely, specific inhibition of MMP9 using the highly selective, cell-permeable, and reversible MMP9 inhibitor (AG-L-66085) reduced the contractile response in myometrial tissues from pregnant women. We observed a reduction in the oxytocin-induced contractile response over time as indicated by area under the curve, ($p<0.0001$) and a reduction in contraction amplitude ($p<0.01$) in AG-L-66085-treated tissues compared to controls. For spontaneous contractions, the addition of AG-L-66085 led to a reduction in the area under the curve ($p<0.05$) and a reduction in contraction amplitude ($p<0.05$).

Conclusion: These data support the hypothesis that elevated MMP9 observed in laboring myometrial tissue promotes uterine contraction and preterm labor, while MMP9 inhibition promotes uterine relaxation. The observed effects are not specific to oxytocin-mediated contractions.

Perceptions of Caring and Mental Health in LGBTQ+ Youth in Foster Care

Grey Raber, Princeton University
NICHD
Poster 149
gfraber@princeton.edu

Research has indicated that the mental health concerns of foster youth tend to be much greater than those of youth not in foster, and that these concerns tend to be even greater for LGBTQ+ youth in care. In this study we compared the relationship between foster care and mental health concerns among LGBTQ+ and cisgender, heterosexual youth. We also studied foster youth's perceptions of caring relationships, and the relationship between these perceptions and mental health concerns, among LGBTQ+ and cisgender, heterosexual youth. Data came from the 2016 and 2019 Minnesota Student Survey. 134,744 ninth- and eleventh- grade students, 1,869 of whom were in foster care, were included. We used linear and logistic regression to analyze how LGBTQ+ and foster status related to mental health concerns and how LGBTQ+ identity and perceived caring related to mental health concerns in the foster sample. We used t-tests to compare perceived caring in LGBTQ+ and cisgender, heterosexual youth in foster care. In these analyses, foster care was more consistently linked to mental health concerns among cisgender, heterosexual youth than LGBTQ+ youth, although LGBTQ+ youth had greater mental health concerns, overall. Perceptions of caring, which were lower in LGBTQ+ than cisgender heterosexual foster youth, were associated with reduced mental health concerns. Even when controlling for perceptions of caring, however, LGBTQ+ identity was strongly related with mental health concerns among youth in foster care. These results help us to better understand the mental health concerns of LGBTQ+ youth, particularly LGBTQ+ youth in foster care, and the role of caring relationships in these youth's lives.

Role of S-Nitrosation in the Mechanism of Nitric Oxide-mediated Relaxation of Human Myometrium

Mairani Ramirez, University of Nevada, Reno
NICHD
Poster 150
mairanir@unr.edu

Preterm labor affects ~10% of all pregnancies in the United States. Nitric oxide (NO) is a critical driver of relaxation in the uterus during pregnancy, yet in the smooth muscle of the uterus, or myometrium, NO does not relax the tissue in the same way as other tissues. We have found that the posttranslational modification S-nitrosation (SNO), in which an NO group binds to a thiol side chain of a cysteine residue on a protein, is a key modulator of relaxation in the myometrium. The full effects of SNO on the cellular machinery of contraction, specifically smooth muscle actin (SMA), remain unclear. SMA plays a pivotal role in muscle contraction through the binding of myosin heads to actin filaments to achieve a contraction. In this study, we aimed to elucidate the influence of S-nitrosation on SMA. An actin motility assay, which visualizes actin-myosin dynamics, was performed to determine the changes in actin velocity after actin [0.15 μM] and myosin [100 μg/mL] were individually treated with glutathione (control) [50 μM] or s-nitrosoglutathione (nitric oxide donor) [50 μM]. Though these results were not significant ($p=0.567$, $n=3$), possibly due to the low 'n,' it is possible to consider S-nitrosation as a potential regulator of muscle contraction, offering insights into possible therapeutic effects for women experiencing preterm labor.

Disparities in Motor Vehicle Crash Fatalities Among High-Risk Teen Drivers

Dominique Rose, Nationwide Children's Hospital
NICHD
Poster 151
dominique.rose@nationwidechildrens.org

Purpose: Existing research recognizes the critical role age plays on motor vehicle crashes, but few have examined how these factors are related to teen fatalities. This study examined the fatality rates per 100,000 teens and teen drivers aged 15-19 across biological sex, race and ethnicity, using data from the 2015-2020 Fatality Analysis Reporting System (FARS).

Methods: FARS data include all fatal crashes within the U.S. We included two outcomes: (1) fatality among teens aged 15-19 who died regardless of seating position and (2) fatality of teens who were drivers. To evaluate the effect of biological sex, race, and ethnicity on the fatality rate that involved teens, a negative binomial regression was conducted. The analysis was repeated to add sex and race interactions. The same analytic approaches were used for the subgroup of teen drivers.

Results: Of the 14,740 FARS cases included, regardless of seating position, 66% (n=9,776) were male and 54% (n=7944) were drivers. Teen demographics were 52% (n=7,644) Non-Hispanic White, followed by 29% (n=4,233) Hispanic, 15% (n=2,139) Non-Hispanic Black, and 2% (n=254) American Indian and Alaska Native. Compared to Non-Hispanic White teens, American Indian and Alaskan Native teens (RR= 2.07; CI=1.59-2.69) had a higher risk of dying in a crash, while Non-Hispanic Asians (RR 0.34; CI= 0.26-0.44) had a lower risk of crash fatality. Compared to Non-Hispanic White teen drivers, Non-Hispanic Black teen drivers had a significantly lower risk for crash fatalities (RR=0.74; CI=0.67-0.83).

Conclusion: American Indian and Alaskan Native teens have the highest annualized sex-race-adjusted crash fatality requiring immediate attention. Future studies should address these factors by developing tailored interventions for this high-risk population.

Significance/Contribution: Traffic fatalities are a preventable public health challenge. These results highlight inequities that contribute to the increased risk of fatal crash fatalities among teen drivers in minority groups.

Associations of Adverse Childhood Experiences (ACEs) with Stress Biomarkers and Depression

Rebekka Twine, University of California, Davis
NICHD
Poster 152
rtwine@ucdavis.edu

Adverse childhood experiences (ACEs) are traumatic events that occur during childhood, such as physical abuse, sexual abuse, or witnessing domestic violence. Previous research indicates that ACEs can lead to multiple negative health consequences and elevated risk of depression, but the biological mechanisms underlying these effects are not known. We examined associations between ACEs (ACE score), depressive symptoms, and stress-related biology, with a focus on inflammation, autonomic nervous system physiology, and cortisol levels. Preliminary analyses are based on the ongoing Social Disconnection Study (expected n = 280), focusing on adolescence, a developmental period of elevated risk for the onset of mood disorders. The sample size used for the analyses is 155 adolescents between the ages of 11 and 15 years old (M = 13.48 years, SD = 1.22). Understanding the connection between ACEs and stress-related biology in adolescence will provide insights into possible biological mechanisms underlying the consequences of childhood adversity.

Investigating Medical Mistrust Amongst Pregnant and Perinatal Women

Evangeline Warren, The Ohio State University
NICHD
Poster 153
warren.651@osu.edu

Reviews of medical mistrust literature have underscored a need for further qualitative analysis to better document the role of medical mistrust as a mediating variable. Medical mistrust is increasingly prevalent in minoritized communities, many of which have a historically fraught relationship with medical institutions. Medical mistrust also has been associated with delayed entry into care, which is of particular importance in prenatal care. To study these related issues, we conducted interviews with 37 pregnant or recently pregnant women from diverse backgrounds. We organize our findings according to three foci of interest in the interviews. These topics are: (1) building strong provider/patient relationships in the face of mistrust, (2) locating the point of rupture for trust, and (3) mitigating the development of mistrust when a rupture occurs.

Healthcare Providers' Perceptions of Digital Health Devices for Management of Pediatric Sepsis in Bangladesh

Alicia Genisca, Warren Alpert Medical School of Brown University
FIC
Poster 154
alicia.genisca@brownphysicians.org

Background: Sepsis, a life-threatening condition, disproportionately affects populations in low and middle-income countries (LMICs). Septic children in LMICs face high mortality rates, with early detection and clinical monitoring posing a significant challenge. There is great potential for wearable digital health devices and mobile clinical decision support (CDS) tools to enable closer monitoring and more prompt recognition of children at risk of sepsis for health care providers (HCPs).

Methods: Between February and May 2024, we conducted 18 individual, semi-structured, in-depth interviews with HCPs at three hospitals in Bangladesh. Applied thematic analysis was applied to analyze HCPs experience caring for pediatric sepsis. Framework matrix analysis was used to analyze perceptions of use of wearable digital health devices for the management of pediatric sepsis.

Results: Facilitators to sepsis management included minimal patient costs for sepsis care and experience-sharing sessions on case management. Challenges to sepsis management included insufficient patient beds, limited physical space, and lack of essential resources. HCPs believed these CDS tools could enhance patient care by reducing management time and aiding in faster clinical decision-making, with some suggesting it could lower mortality rates. Concerns regarding implementation included internet availability and affordability of the wearable devices.

Conclusion: The study highlights the need for adequate training and improved monitoring in resource-limited hospitals to strengthen sepsis management and reduce pediatric mortality in LMICs. It also emphasizes the potential of CDS tools to improve outcomes, while addressing implementation challenges for effective integration into healthcare systems.

Change in the Cortical Motor Maps of Various Hand Muscles Impacted by Stroke with Rehabilitation Intervention

Arianna Alston, Medical University of South Carolina
NICHD
Poster 155
alstonar@musc.edu

Introduction: The corticospinal tract is a neural pathway that plays a vital role in the body's motor function and has been associated with upper extremity (UE) motor recovery after stroke. By utilizing transcranial magnetic stimulation (TMS), the function of the corticospinal tract can be assessed through mapping of the motor cortex by analyzing motor evoked potentials (MEPs). This technique has shown to be promising in assessing the extent of motor recovery in stroke survivors. However, there is a lack of literature that reports on the spatial distinctiveness of motor maps of the multiple muscles responsible for paretic hand motor function. The objective of this research is to determine the effect of rehabilitation intervention on the motor maps of major hand muscles impacted by stroke.

Methods: In a randomized controlled trial, a sample size of 76 stroke survivors will receive 6-week upper limb motor rehabilitation intervention. Participants will be assessed by TMS at baseline, post, and follow-up to identify and evaluate the MEPs of four major hand muscles. Following the identification of the motor maps for the four hand muscles, the spatial overlap of the motor maps among muscle pairs will be quantified. The change in overlap will be statistically analyzed over the assessment times using a repeated- measures ANOVA.

Results: The study is ongoing with continued data collection. Preliminary results will be presented.

Impact: This study will elucidate the effect of rehabilitation intervention on the changes in spatial distinctiveness of motor maps of hand muscles impacted by stroke. The acquired knowledge may provide insight into the mechanisms of motor recovery on a cortical level, thus strengthening the foundational base to develop novel treatments that implicate the role of neuroplasticity in promoting motor recovery.

The Occurrence of and Risk Factors for Clinically Significant Depression in Myocarditis Survivors: Results from an Electronic, Cross-sectional Survey

Jean Marrero-Polanco, Mayo Clinic
NIMH
Poster 156
marrero-polanco.jean@mayo.edu

The life-threatening characteristics of acute myocarditis and its associated long-term morbidity raise the possibility of heightened risk for depression in myocarditis survivors. Yet, depression in myocarditis survivors remains poorly understood. We conducted a cross-sectional study assessing demographics, myocarditis history, cardiac symptom burden, cause of myocarditis, and family history of depression and other mental health conditions. Of the 96 respondents (mean age 41.0 years, 51% women), 43 had clinically significant depression (CES-D total score > 16). Wilcoxon rank-sum tests identified significant anxiety ($p < 4.09E-08$), traumatic stress ($p < 2.32E-07$), reduced quality of life ($p < 5.41E-10$), treatment distress ($p < 5.95E-04$), cardiac symptom burden ($p < 0.002$), general medical morbidity ($p < 2.40E-05$), and lower social support ($p < 1.38E-04$) between depressed and non-depressed myocarditis survivors. Relative importance (RI) analyses using an XGBoost model identified emotional well-being, traumatic stress, general anxiety, and history of depression as top predictors for depression.

Machine Learning Reaction-diffusion Models from Stochastic Dynamics and Spatiotemporal Patterns

Bedri Abubaker-Sharif, Johns Hopkins University
NIGMS
Poster 157
bedri@jhmi.edu

In recent years, live-cell imaging has generated detailed spatiotemporal datasets of biochemical networks within cells. These networks often exhibit characteristics of spatially-distributed excitable systems, with propagating waves of signaling activity that govern processes such as cell migration, division, and other essential physiological functions. Traditionally, these reaction-diffusion systems have been modeled using stochastic partial differential equations incorporating spatial Langevin-type dynamics. Although these knowledge-based models have provided valuable insights, they are typically not directly inferred from experimental data. In this study, we introduce and apply two data-driven methodologies for learning the structure and parameters of spatial Langevin equation (SLE) models: 1) Kramers-Moyal regression to fit microscale stochastic dynamics, and 2) wave features optimization to match macroscale spatiotemporal patterns. As a proof-of-concept, we focus on simulation datasets derived from two stochastic reaction-diffusion models: one based on the FitzHugh-Nagumo equations (FHN model) and another on a biochemically adapted version of the FHN equations (FR model). Our results demonstrate that optimizing stochastic dynamics and spatiotemporal wave patterns enables the accurate estimation of SLE model structure and parameters directly from 1D and 2D spatial data. Furthermore, we show that our approach effectively approximates system behavior, even when working with datasets that have significantly limited temporal resolution and only partially observed molecular components. Overall, this strategy leverages machine learning techniques for robust estimation of reaction-diffusion models from spatiotemporal data, thereby facilitating modeling and understanding of the complex systems that regulate cellular behavior.

Transport of Dynein Dependent mRNA and Protein Cargos in the Drosophila Germline Functions Primarily via Single Activating Adaptor-Bicaudal-D

Phylicia Allen, Medical College of Georgia-Augusta University
NIGMS
Poster 158
phyallen@augusta.edu

Dynein is the microtubule motor responsible for the retrograde transport of most cargo. In vitro studies have shown Dynein requires an activating adaptor to bind cargo and gain motility. However, little is known about Dynein activation on an organismal scale. There are three conserved activating cargo adaptors between Drosophila and humans: BicD, Hook, and Ninein. In flies, depletion of BicD in the female germline results in oogenesis arrest producing a phenotype that is similar to the depletion of Dynein heavy chain. However, neither depletion of Hook nor Ninein results in any oogenesis defect. We therefore hypothesized that BicD is the primary activating adaptor for Dynein in the female germline. To test this hypothesis, we used in vivo proximity biotin ligation to define the Dynein interactome. This analysis revealed a significant enrichment of BicD but failed to identify other conserved activating adaptors. Furthermore, neither Hook nor Ninein was observed within the Dynein interactome in a BicD-depleted background. This suggests that our inability to detect Hook or Ninein is not due to competition among these adaptors for binding to Dynein. To determine whether BicD is uniquely required for localizing cargo within the germline, we used a chimeric construct in which BicD cargos were artificially tethered to Dynein via Hook. This revealed certain cargos were correctly localized by the chimera, whereas others were not. Our results indicate that BicD is the primary adaptor for Dynein in the fly germline and that it is uniquely capable of mediating the correct localization of its cargo.

Novel Micro-ER-phagy Selectively Clears Aberrant Membrane Proteins During Nutritional Stress

Yaneris Alvarado-Cartagena, University of Illinois Chicago
Poster 159
NIGMS
yalvar21@uic.edu

Accumulation of aberrant membrane proteins is associated with human disease. Membrane proteins are inserted first to the endoplasmic reticulum (ER), where two quality-control (QC): ER-associated degradation (ERAD) and macro-ER-phagy, deliver misfolded and excess membrane proteins for degradation in the proteasome and lysosome, respectively. In mutant cells defective in ER-QC, aberrant proteins accumulate. We show that these aberrant proteins are cleared efficiently in the lysosome under nutritional stress through a novel selective micro-ER-phagy pathway, much before a small fraction of normal membrane proteins is degraded via macro-ER-phagy. Moreover, using timelapse 3D microscopy, we demonstrate the dynamics of this under-studied micro-autophagy and show that it occurs within seconds. Importantly, because the processes and signaling pathways explored here are conserved, nutritional stress and the micro-ER-phagy pathway emerge as a way for clearing disease-associated membrane proteins.

Constructing a Proteome-Wide, Harmonizing Database of Ligand-Binding Protein Structures

Kristy Carpenter, Stanford University
NIGMS
Poster 160
kcarp@stanford.edu

Identifying potential ligand-binding pockets on the surface of a target protein is a crucial step in the early stages of drug development. Computational methods present a faster and cheaper way to obtain these pockets than in vitro experiments. There are a plethora of computational methods for pocket identification, including the very recently released AlphaFold3. However, no such method that is freely accessible at scale has entirely solved the pocket-finding problem. There are several common approaches to computational pocket-finding methods, including geometry-based methods, energy-based methods, and template-based methods, each of which has different strengths and weaknesses. To unify these diverse pocket predictions and streamline the target identification process, we introduce the Human Omnibus of True and Predicted Pockets, a database that curates and harmonizes pockets predicted by diverse computational methods for the whole human proteome. Beyond simply aggregating pocket predictions, this work highlights the intrinsic differences between pocket-finding methods, presents an estimate of the size of the druggable proteome, and provides a proteome-wide pocket structure dataset designed for ease of use in machine learning applications.

Genetic Underpinnings of Natural Variations in Stress

Stefan Choy, Lehigh University
NIGMS
Poster 161
stc221@lehigh.edu

Chronic stress in humans has been linked to many adverse health traits, such as high blood pressure, anxiety, and depression. While stress responses vary widely between individuals and across species, little is known about the genetic basis of natural variation in stress responses. Thus, there is a critical need to employ models to better understand the genetic underpinnings of stress. To this end, we utilize the model organism Astyanax mexicanus, or the blind Mexican cavefish. A. mexicanus exists as interfertile populations of riverine surface fish and over 35 populations of cave fish. The cave populations have repeatedly evolved characteristic cave traits, such as eye degeneration and albinism, but have also evolved changes in behavior, including a reduced stress response. The genetic and molecular basis for stress is conserved across taxa with many key regulators of stress being shared between A. mexicanus and humans, enabling A. mexicanus as a powerful model for studying evolved reductions in stress. Here, we quantified stress responses across hybrid fish by crossing surface fish and cavefish from the Tinaja, Molino, and Pachón caves. We assessed whether differences in stress responses and other cave-evolved traits correlate to determine if these traits could share a genetic basis. These data better our understanding of the genetic underpinnings of stress and provide a basis for future work on determining the functional basis of stress reduction.

Reproductive System Aging in the Canonically "Non-aging" C. Elegans Dauer

Fred Koitz, University of North Carolina at Chapel Hill
NIGMS
Poster 162
fkoitz@unc.edu

The C. elegans dauer larval stage is induced by early life stress and is a diapause state in which development–and, apparently, aging–ceases. It is not just increased lifespan, but the preservation of reproductive ability after recovery from dauer that makes dauer adaptative. However, animals that spend longer periods in dauer have been shown to have a higher incidence of later reproductive defects and reduced fertility, which argues against the paradigm that dauers are "non-aging."

We set out to identify reproductive system changes during dauer that could explain this post-dauer reproductive defect using live imaging of animals to examine changes to the reproductive system over the span of four weeks in diapause. Surprisingly, we discovered that the germline can experience dramatic changes over extended diapause. An increase in dauer duration is correlated to both a reduction in germ cell number as well as overall gonad size. Germline shrinking isn't a feature inherent to all dauers, as dauer-constitutive genetic mutants, daf-2(e1370) and daf-7(e1372), fail to shrink their germlines at the restrictive temperature. However, these mutants shrink their germlines at the permissive temperature when exposed to natural dauer-inducing conditions. Therefore, germline shrinking is not an inherent part of dauer but is, rather, dependent on the inducing conditions in which the dauer is formed. While dauers may be "non-aging" on an organismal level, our work shows that the dauer can age on a cellular and tissue level.

Development of α3β4 Nicotinic Acetylcholine Receptor-targeted Aristotelia Alkaloid Derivatives for Substance Use Disorder Treatment

Ana Lopez-Hernandez, University of Illinois Chicago
Poster 163
NIGMS
alope204@uic.edu

Nicotinic acetylcholine receptors (nAChRs) are a family of ligand-gated ion channels implicated in various central nervous system disorders and diseases. Given the high demand for treatments targeting substance use disorders, there has been growing interest in investigating α3β4 nAChRs, which are found in brain regions implicated in drug addiction. Work by our lab and others has identified aristoquinoline, an alkaloid found in Aristotelia chilensis, as a moderately selective inhibitor of α3β4 nAChRs. To understand the structure-activity relationship (SAR) between aristoquinoline and α3β4 nAChRs, we synthesized and assessed a series of aristoquinoline derivatives. This work revealed SAR patterns that yielded compounds with enhanced potency against α3β4 nAChRs. Subsequent mechanism-of-action studies indicated that these compounds act as non-competitive allosteric modulators of α3β4 nAChRs. Furthermore, in an animal model of cocaine relapse, our findings demonstrate that aristoquinoline significantly diminishes drug-seeking behaviors. These results provide additional support for the involvement of α3β4 nAChRs in the addictive properties of cocaine and highlight the potential therapeutic value of aristoquinoline derivatives in addressing substance use disorders.

Biocatalytic Diversification of Terpenoids Using a Cytochrome P450 Targeted Genome Mining Approach

Caitlin McCadden, University of Florida
NIGMS
Poster 164
cmccadden@ufl.edu

Biocatalysis employs both in vitro enzymes and whole-cell methods to access synthetically challenging molecules and key intermediates and to derivatize drug analogs. Cytochromes P450 (P450s) are amongst the most superlative and versatile oxidative enzymes found in nature. While P450s have been investigated extensively in humans, the characterization and catalytic scope of bacterial P450s remain underexplored in comparison to the number predicted in genomic databases. Utilizing a genome mining approach, we initiated an in vivo screen to probe the biocatalytic functionality of predicted P450s from Streptomyces with the bioactive diterpenoid abietic acid. In doing so, we elucidated the structures of several bioactive derivatives from different strains, including four products that are novel to bacteria. Amongst notable conversions observed in the study was that of abietic acid to 15-hydroxy-7-oxo-8,11,13-abietatrien-18-oic acid, 4, which involves both dehydrogenation and multiple hydroxylation reactions. Hydroxylation is a commonly observed P450-catalyzed reaction, while dehydrogenation is comparatively less explored, especially in biosynthetic and mechanistic terms. This compound is synthetically sought after for its wide range of biological activities. The findings from this study are expected to assist in building a more complete understanding of P450 enzymology and provide access to abietane derivatives that can be used to guide future efforts in genome mining, green chemistry, enzymatic synthesis, and drug discovery.

Identification and Functional Characterization of lncRNAs involved in Human Monocyte-to-Macrophage Differentiation

ChristyMontano, University of California, Santa Cruz
NIGMS
Poster 165
cmontan3@ucsc.edu

One in four children with leukemia has acute myeloid leukemia (AML), which occurs when myeloid cells, such as monocytes, do not differentiate into macrophages. While significant progress has been made in the diagnosis of AML, research has been focused on the protein-coding genes involved. Still, much remains unknown regarding the development and molecular mechanisms underlying AML. Knowing that <2% of the human genome encodes for protein-coding genes, while over 85% is transcribed into RNA, we are interested in understanding the role that noncoding RNA plays within myeloid cells. LncRNAs represent the largest group of RNA produced from the genome and are very cell-type specific in expression, yet only 3% have ascribed functions. Hence, there is a fundamental gap in our understanding of how lncRNAs regulate processes such as monocyte-to-macrophage differentiation.

Although the role of protein-coding genes in macrophage biology has been studied extensively, our understanding of the role played by lncRNAs in this context is still in its early stages. There are over 20,000 lncRNAs in the human genome. Therefore, attempting to select a lncRNA to characterize functionally can be a challenge. We have described two approaches to identify and functionally characterize lncRNAs involved in monocyte-to-macrophage differentiation. The first involved using RNA-seq to infer possible functions, and the second involved a high throughput functional screen. We examine the advantages and disadvantages of these methodologies and the pipelines for validation that assist in determining functional lncRNAs.

Impostor Phenomenon and Emotional Cost as Predictors of Biomedical Research Career Intentions

Madeline O'Grady, University of Texas at Austin
NIGMS
Poster 166
madelineogrady@utexas.edu

Biomedical research trainees face a multitude of barriers in their educational journey, with many leaving research pathways despite extensive preparation. Two threats to their persistence explored in this paper are the impostor phenomenon (IP) and the emotional cost of continuing. Bivariate correlations and simple and multiple linear regression models were conducted to examine the relationship between these threats and intentions to pursue a career in biomedical research. Both IP and emotional cost uniquely predicted trainee intentions to drop out of research career paths. The relationship between emotional cost and intentions to pursue a biomedical research career was moderated by trainees who reported higher (vs. lower) levels of fixed mindset. The paper explores implications and future directions.

Circadian Rhythms Mediate Malaria Transmission Potential

Brianna Parrington, Rijo-Ferreira Lab | University of California, Berkeley
NIGMS
Poster 167
parrington_brianna7@berkeley.edu

Malaria transmission begins when infected female Anopheles mosquitos deposit Plasmodium parasites into the mammalian host's skin during a bloodmeal. The salivary gland-resident sporozoite parasites migrate to the bloodstream, subsequently invading and replicating within hepatocytes. As Anopheles mosquitos prefer biting at night, with a 24-hour rhythm, we investigated whether their salivary glands are under circadian control, anticipating bloodmeals and modulating sporozoite physiology for host encounters. Here we show that approximately half of the mosquito salivary gland transcriptome, particularly genes essential for efficient bloodmeals such as anti-blood clotting factors, exhibits circadian expression rhythms. Notably, even though sporozoites are considered quiescent parasite forms, a substantial subset of their transcriptome shows daily rhythms of expression. These include genes involved in parasite motility, potentially modulating its ability to initiate infection at different times of day. Our findings suggest a circadian evolutionary relationship between the vector, parasite and mammalian host. Contrary to the belief that sporozoites are quiescent, our results show that they are transcriptionally active, displaying daily rhythms, preparing sporozoites to efficiently infect the mammalian host at specific times of the day.

Selection for Faster Expansion on a Surface Causes a Pseudofilamentous Phenotype

Katie Randolph, Cornell University
NIGMS
Poster 168
ker234@cornell.edu

Spatially structured microbial populations are ubiquitous in nature and display evolutionary dynamics that are not yet well characterized, despite their importance to human health and technology. We performed an evolutionary experiment with the budding yeast Saccharomyces cerevisiae to investigate how cells evolve when selected for surface-associated growth and expansion. We found that cells selected for faster expansion on surfaces evolved an elongated cell shape and a bipolar budding pattern, in which daughter cells bud at the pole opposite to the birth scar, rather than near the birth scar as ancestor daughter cells. Interestingly, these phenotypes mimic filamentous growth—a non-heritable differentiation behavior displayed in response to starvation in many fungi, including Saccharomyces, that is thought to enable faster exploration of space. Our evolution experiment produced a phenotype akin to filamentous growth, obtained via heritable evolutionary adaptation instead of phenotypic differentiation. By comparing the genotypes of the experimental group with the control and ancestor groups, we have identified putative, causative mutations that we are now engineering into the wildtype to confirm causation for each phenotype of interest. Putative, causative mutations appear in genes involved in cell cycle progression, establishment of cell polarity during budding, and metabolism. Future work will investigate the physical and mechanical changes evolved at both the single-cell and colony scales that enable faster expansion and modulation of the relative strengths of genetic drift and natural selection. Taken together, these data will provide a comprehensive understanding of how evolution acts on single-cell and colony traits to adapt to surface-associated growth.

Inducing Pyrrole Rearrangements for Chromophore Development

Cesar Reyes, University of Southern California
NIGMS
Poster 169
careyes@usc.edu

Molecular photoswitches that harvest light to induce changes at the molecular level have been broadly used in numerous fields. The development of photoswitches that absorb low energy light is of notable interest due to the growing demand for smart materials and therapeutics necessitating benign stimuli. Donor-acceptor Stenhouse adduct (DASA) molecules are a relatively new class of photoswitches that respond to light in the visible to near-infrared spectrum. Despite breakthroughs in modularity for the donor, acceptor, and triene structural compartments, the DASA backbone heteroatom has remained static due to synthetic challenges. We provide a predictive tool and strategy to vary the heteroatom, introducing amino DASA photoswitches. Synthesis of amino DASAs allowed the analysis of backbone heteroatom effects on photophysical properties. Amino DASA synthesis is enabled by an aza-Piancatelli rearrangement on pyrrole substrates, breaking aromaticity and capitalizing on the inductive properties of sulfonyl groups. The pyrrole aza-Piancatelli rearrangement has also been applied towards the synthesis of amino Stenhouse salt streptocyanine dyes that display excellent free-base stability and photoresponsive activity. These studies provide a framework for the continued development of visible light absorbing molecular photoswitches.

Effects of Escherichia coli Domain IV EF-G Mutations on Protein Activity and Reading Frame Maintenance

Jacob Steele, University of Houston
NIGMS
Poster 170
jsteele993@gmail.com

Authors: Jacob H. Steele1, Yanjun Chen2, Shoujun Xu2, Yuhong Wang1

Affiliations:
1. Department of Biology and Biochemistry, University of Houston, TX
2. Department of Chemistry, University of Houston, TX

The ribosome is a ribonucleoprotein complex consisting of two subunits. It contains three tRNA binding sites: the A-, P-, and E-site. During protein synthesis, the ribosome decodes mRNA one codon at a time, facilitated by a translocase enzyme, elongation factor G (EF-G). Two residues (Q508 and H584) in the domain IV region of EF-G play important roles in the induction of translocation as they interact with codon-anticodon minihelix formed between mRNA and the A-site tRNA. The primary goal of this project is to reveal the function of EF-G mediated translocation via mutagenesis of these two residues and determine their effects on force generation. Five EF-G point mutations were successfully produced, and the proteins purified. Biological assays have shown that all five mutations bind and hydrolyze GTP at similar rates, suggesting that GTPase activity has not been compromised by the substitutions. The translocase activity of two mutants, Q508K and H584K, has been measured using force-induced remnant magnetization spectroscopy (FIRMS). While Q508K maintains the proper 3 nucleotide (nt) reading frame, H584K appears to result in a -1 nt frameshift. In addition, single molecule fluorescent resonance energy transfer (sm-FRET) experiments are currently being performed to determine the conformational change of the EF-G mutants and FIRMS will be utilized to determine the mutation effects on force production. We expect that the remaining EF-G mutants will be able to complete partial translocation and have a reduction in force exertion. Taken together, this would show that Q508 and H584 are crucial in the generation of a power-stroke which is essential to maintain translocation fidelity during EF-G mediated translocation.

Reconstitution of Dictyostelium Discoideum Contractility Kits

Brooke Waechtler, Johns Hopkins
NIGMS
Poster 171
bwaecht1@jh.edu

The cell's ability to undergo shape change is a central feature in many cellular processes, including cytokinesis, motility, migration, and tissue formation. To make these shape changes, the cell harnesses the contractility machinery, which is poised to sense and respond to mechanical cues from its environment. In Dictyostelium discoideum, these proteins construct large-scale assemblies at the cell cortex to give the cell its shape. These proteins also preassemble in the cytoplasm, forming protein complexes or condensates that we have termed Contractility Kits (CKs). Cells build two types of CKs: the mechanoresponsive and the non-mechanoresponsive. The mechanoresponsive CK components accumulate at sites of mechanical stress. Non-mechanoresponsive CK components antagonize the mechanoresponsive CKs. The preassembly of distinct contractility proteins into CKs likely allows for the delivery of important cytoskeletal proteins to the cortex quickly and synchronously in response to mechanical cues. Although we have a good understanding that these proteins do interact, currently, little structural information exists about how these CKs are formed and which proteins directly interact. To determine the structure of these CKs, I am using a reductionist biochemical approach to see which CK proteins directly interact with each other. Specifically, I am purifying multiple proteins within the contractility system (fluorescently tagged Myosin II, Cortexillin I, Discoidin 1, IQGAP1, and IQGAP2) and will determine the KD between these proteins. Using these purified proteins, I have found that Cortexillin I-actin crosslinking is enhanced at a lower pH. The addition of Discoidin I to this system increases this actin crosslinking and bundling at a pH of 5.8 and 6.0; however, Discoidin I decreases Cortexillin I-actin crosslinking at a pH of 6.2. Since pH affects the interactions between actin, Cortexillin I, and Discoidin I, we have hypothesized that there could be a pH gradient between the cytoplasm and the cortex. Specifically, we hypothesize that the cytoplasm has a slightly higher pH, allowing for CK formation, while the cortex has a slightly lower pH, allowing for CK disassembly and actin binding. By uncovering the molecular mechanisms of cellular mechanics, we will develop a deeper understanding of a wide range of biological processes and facilitate future biological engineering.

The Neural Systems and Real-world Mood Dynamics Underlying Dispositional Risk for Internalizing Illness

Shannon Grogans, University of Maryland
NIGMS
Poster 172
sgrogans@umd.edu

Background: Internalizing disorders impose a staggering burden on public health. Existing interventions are inconsistently effective, underscoring the need to understand the mechanisms that confer risk. Neuroticism/negative emotionality (N/NE) is a well-established risk factor for future anxiety and depression diagnoses. Yet, the neural systems and real-world psychological processes underlying these prospective-longitudinal trajectories remain unclear.

Method: We addressed these questions using a novel combination of data—including threat-anticipation and emotional-face fMRI paradigms and repeated waves of smartphone experience-sampling and internalizing symptom assessments—acquired from an ethnoracially diverse, risk-enriched sample of emerging adults followed for 2.5 years (n=217-220; ps<.05).

Results: Robust general linear model (GLM) analyses demonstrated that elevated baseline N/NE was associated with longitudinal increases in internalizing symptoms. Variation in the N/NE phenotype was uniquely associated with heightened bed nucleus of the stria terminalis (BST) reactivity to uncertain-threat anticipation, and unrelated to BST/amygdala reactivity to certain-threat anticipation or negative faces. Hierarchical linear modeling (HLM) analyses demonstrated that N/NE was associated with elevated levels of tonic (stressor-independent) and reactive (stressor-dependent) negative affect, whereas BST reactivity to uncertain-threat was selectively associated with heightened stressor reactivity.

Discussion: These observations provide a first glimpse at the processes that link a prominent dispositional risk factor to the emergence of internalizing illness. They suggest that elevated levels of the risk-conferring N/NE phenotype reflect exaggerated BST threat-reactivity, which manifests as potentiated reactivity to everyday stressors and challenges. These observations provide a neurobiologically grounded framework for conceptualizing internalizing illness and prioritize mechanistic work focused on the BST. A relatively large, well-characterized sample enhances confidence in the robustness of these findings.

Reward Sensitivity, Pubertal Development, and Circadian Rhythm

Mackenzie Maddox, Temple University
NIGMS
Poster 173
mack.maddox@temple.edu

Early-onset bipolar spectrum disorders (BSD) are associated with more severe prognoses, including greater comorbidity, increased rates of rapid cycling, and greater risk for suicidality. Adolescence is a crucial developmental period that includes changes in the reward and circadian systems. Reward and circadian rhythms both have been linked to BSD independently, in that those diagnosed with BSD tend to display a hypersensitivity to reward and also have irregular circadian rhythms. However, less is known about the associations between the reward system and circadian disruption preceding onset. The goal of this study was to elucidate potential associations between trait reward sensitivity and circadian disruption while examining the moderating impact of pubertal development. Participants were a community-based sample of adolescents (n = 314, 56.7% Female, 57.6% White) recruited from the Philadelphia area for longitudinal studies assessing risk factors for first-onset depression and BSD. During screening phases, participants completed the Behavioral Activation System scale (BAS) as an indicator of trait reward sensitivity. Concurrently at baseline, participants completed the Pubertal Development Scale (PDS) and one week of actigraphy (Actiwatch). Non-parametric circadian analyses were conducted using the 'nparACT' package in R to generate three circadian indices: relative amplitude (RA), intradaily variability (IV), and interdaily stability (IS). We predicted higher BAS would be associated with greater circadian disruption as indicated by a flatter RA, a lower IS, and a higher IV. Given that puberty has been associated with changes in reward responsiveness and circadian functioning, we also predicted that greater pubertal development would amplify these associations. Hierarchical multiple regression was used to examine main and interaction effects across three models while controlling for related covariates. Consistent with our hypotheses, higher BAS was significantly associated with lower IS ($B = -0.005$, $p < .01$), and greater pubertal development amplified this association ($B = -0.002$, $p < .01$) after controlling for race and biological sex. Simple slopes revealed that this negative association was seen at both advanced and moderate stages of pubertal development but not at early stages. Although there was not a significant main effect between trait reward sensitivity and RA, there was a significant interaction involving pubertal development ($B = -0.002$, $p < .01$) after controlling for race and biological sex. Specifically, higher trait reward sensitivity was significantly associated with a flatter RA among those who were in later stages of pubertal development. BAS was not associated with IV, alone or in interaction with pubertal development. These findings show that circadian patterns of instability observed in clinical populations (e.g., individuals with BSD) also were present in a non-clinical sample of adolescents with elevated reward sensitivity, an established risk factor for BSD. It is possible that these interactive effects between reward and circadian rhythms may contribute to the increased incidence of mental health difficulties in adolescence. More longitudinal research is needed to evaluate this possibility.

Amygdala Crh Cell Activity Required for Territorial Aggression

Khalil Threadgill, McLean Hospital, Harvard Medical School
NIGMS
Poster 174
kthreadgill@mclean.harvard.edu

Authors: Khalil J. Threadgill1, Emily L. Newman1, Kerry J. Ressler1

Affiliations: Psychiatry, McLean Hospital, Belmont, MA; Harvard Medical School, Boston, MA

Introduction: Exposure to trauma can lead to posttraumatic stress disorder, which can be accompanied by increases in emotional reactivity and aggression. The central amygdala (CeA) is a point of intersection for threat and aggression neurocircuitry, and corticotropin releasing hormone (Crh)-expressing CeA cells are necessary for adaptive active threat responding. The present study uses chemogenetics in mice to examine the role of Crh+ CeA neurons in territorial and self-defensive inter-male aggression.

Materials and Methods: Male CRH-ires-Cre mice were tested for aggression every other day for two weeks. During these 5-min resident-intruder confrontations, a submissive intruder male was placed into the territory of the aggressive resident CRH-ires-Cre male and aggressive behavior was quantified as latency to the first bite and total bite frequency. Aggressive resident males received intra-CeA adeno-associated virus (AAV) for Cre-dependent expression of designer receptors activated exclusively by designer drugs (DREADDs; hM3Dq, hM4Di) or control virus in Crh+ CeA neurons. After recovering from surgeries, mice were tested for aggression after receiving systemic vehicle or deschloroclozapine (DCZ) for chemogenetic manipulation of Crh+ CeA neurons. Territorial aggression tests were conducted using submissive intruders and self-defensive aggression tests were conducted using aggressive intruders.

Results: Chemogenetic inhibition of Crh+ CeA cells blocked aggression in territorial aggression tests, but did not block self-defensive retaliation during self-defensive aggression tests. Chemogenetic activation of Crh+ CeA cells increased aggression.

Conclusion: Crh+ CeA cell activity is necessary for aggressive behavior onset in mice. Crh+ CeA neurons may serve as a therapeutic target to treat aberrant, offensive aggression with improved behavioral selectivity.