The Evelyn F. McKnight Brain Research Foundation Poster Reception

Loews Chicago Hotel
Wright Rooms 1-2-3
455 North Park Drive
Chicago, IL 60611

Sunday, October 20, 2019
5:00 p.m. – 7:00 p.m.

Dedicated to the Understanding and Alleviation of Age-Related Memory Loss

THE McKNIGHT BRAIN RESEARCH FOUNDATION®
Preserving memory, enhancing life

McKNIGHT BRAIN INSTITUTES

UNIVERSITY OF ALABAMA AT BIRMINGHAM • UNIVERSITY OF ARIZONA • UNIVERSITY OF FLORIDA • UNIVERSITY OF MIAMI

www.tmbrf.org

Special thanks

to the

McKnight Brain Research Foundation

for making

this event possible!

McKnight Brain Research Foundation
Board of Trustees

Michael L. Dockery, M.D.
Chair
Charlotte, North Carolina

Richard S. Isaacson, M.D.
New York, New York

Susan L. Pekarske, M.D.
Tucson, Arizona

Gene G. Ryerson, M.D.
Gainesville, Florida

Madhav Thambisetty, M.D., Ph.D.
Ellicott City, Maryland

Robert M. Wah, M.D.
McLean, Virginia

J. Lee Dockery, M.D.
Chair Emeritus
Gainesville, Florida

Nina Ellenbogen Raim, M.D., J.D.
Trustee Emerita
Miami Beach, Florida

Melanie A. Cianciotto
Corporate Trustee
SunTrust Bank, Orlando, Florida

Amy Porter
Executive Director
Alexandria, Virginia

Institutional Directors

- **Evelyn F. McKnight Brain Institute**
  University of Miami - (Established 1999)

Executive Director	Ralph Sacco, M.D.
Scientific Director	Tatjana Rundek, M.D., Ph.D. Evelyn F. McKnight Chair for Learning and Memory in Aging

- **Evelyn F. and William L. McKnight Brain Institute**
  University of Florida - (Established 2000)

Executive Director	Todd Golde, M.D., Ph.D.
Deputy Director	Steven DeKosky, M.D.
Chair for Aging & Memory	Tom Foster, Ph.D. Evelyn F. McKnight Chair for Research in Cognitive Aging and Memory
Chair for Clinical Translational	Ronald Cohen, Ph.D. Evelyn F. McKnight Chair for Cognitive Aging and Memory Clinical Translational Research

- **Evelyn F. McKnight Brain Institute**
  University of Alabama at Birmingham - (Established 2004)

Director	Ronald Lazar, Ph.D. Evelyn F. McKnight Chair for Learning and Memory in Aging
Associate Director	Erik Roberson, M.D., Ph.D.

- **Evelyn F. McKnight Brain Institute**
  University of Arizona - (Established 2006)

Director	Carol Barnes, Ph.D. Evelyn F. McKnight Chair for Learning and Memory in Aging
Associate Director	Lee Ryan, Ph.D.

MBRF Poster Session Author and Title List

University of Miami

1.	Danylo Cabral, Jordyn Rice, Christina Nunez, Danielle Abel, Kaylee Van Deusen, Baabak Moustafi, Marcela Kitaigorodsky, David Loewenstein, Lawrence Cahalin, Tatjana Rundek, Joyce Gomes-Osman "Exercise Barriers, Motivators, and Self-efficacy in Sedentary Aging Adults: An Ongoing Trial"
2.	Danylo Cabral, Jordyn Rice, Christina Nunez, Danielle Abel, Kaylee Van Deusen, Baabak Moustafi, Marcela Kitaigorodsky, David Loewenstein, Lawrence Cahalin, Tatjana Rundek, Joyce Gomes-Osman "Effects of 8-weeks of Aerobic Exercise Intervention on Fitness and Neuroplasticity in Aging Adults: Preliminary Results of an Ongoing Trial"
3.	Sunjoo Cho, Ashish K. Rehni, Hever Navarro Quero, Carolyn J. Keatley, Shyam Gajavelli, Sebastian Koch, Yeon S. Ahn, Miguel A. Perez-Pinzon, Wenche Jy, Kunjan R. Dave "Red blood cell-derived microparticles treatment improves post-intracerebral hemorrhage in long-term outcomes in rats."
4.	Krizia Crespo, Sonya Kaur, Katalina McInerney, Joshua Rooks, Marina Sarno, Mitchell Slugh, Sarah Getz, Annelly Bure-Reyes, Nikhil Banerjee, Tatjana Rundek, Bonnie Levin "Ethnicity moderates the relationship between sleep quality and learning and memory."
5.	Sarah J. Getz, Johnus Rooks, Katalina F. McInerney, Nikhil S. Banerjee, Bonnie E. Levin "Fatigue, Adverse Childhood Experiences, and Frailty in Later Life"
6.	Ami P. Raval, William Javier Moreno, Juliana Sanchez, Nadine Kerr, Ofelia E. Furones-Alonso, W. Dalton Dietrich, Helen M. Bramlett "Chronic nicotine exposure hinders whole body vibration therapy induced ischemic protection in the brain of reproductively senescent female rats"
7.	Varun Reddy[1], Concepcion Furones[1], Juan Pablo de Rivero Vaccari[2], Ami Raval[1] "Effects of endogenous estrogen fluctuations on the post-ischemic innate inflammation in the brain of female rats."
8.	Ashish K. Rehni, Sunjoo Cho, Kunjan R. Dave "Prior exposure to recurrent hypoglycemia causes post-ischemic ER stress via increased free radical production in treated diabetic rats."
9.	Joshua Rooks J., Banerjee, N., Goodman, Z., McInerney, K. F., Sarah Getz, S. Kaur, and Bonnie Levin "Measuring Frailty in Middle and Later Years and its Association with Cognition"
10.	Sharnikha Saravanan, Concepcion C Furones, Weizhao Zhao, Kunjan R Dave, Miguel A Perez-Pinzon, Ami P Raval "Post-stroke physical exercise reduces ischemic brain damage and improves cognition in reproductively senescent female rats"

University of Florida

11.	Jolie Barter, Ashok Kumar, Julie A. Stortz, McKenzie Hollen, Dina Nacionales, Philip A. Efron, Lyle L. Moldawer, and Thomas C. Foster "Age and Sex Influence the Hippocampal Response and Recovery Following Sepsis"
12.	Blaes, S.L., Orsini, C.A., Holik, H.M., Wilson, J., Singhal, S.M., Frazier, C.J., Bizon, J.L., Setlow, B. "Regulation of risky decision making via activity in dopaminergic neurons in the ventral tegmental area."
13.	P. Bose, J. Hou, S. Tsuda, R. Nelson, D. Plant, R. J. Bergeron, F. J. Thompson "A potential experimental therapy for TBI-induced disabilities in a rodent model"
14.	Brittany DeFeis, Jared Tanner, Deirdre O'Shea, Liselotte De Wit, Andrea Mejia, Priscilla Amofa, Sonnie Mayewski, Melanie Chandler, Glenn Smith "Mediation of periventricular white matter hyperintensity burden, cognition, depression, and quality of life in older adults with amnestic Mild Cog Impairment"
15.	N.M. DiCola, A.L. Lacy, O.J. Bishr, K.M. Kimsey, K. Diba, S.N. Burke, A.P. Maurer "Age-Related Decreases in CA3-CA1 Ripple Coordination"
16.	Matteo Grudny, S. Nuner, M. Pompilus, A. Dunn, M. Feb, C. C. Kaczorowski "Genetic diversity differentially impacts diffusion MRI measures in cortex and hippocampus of wildtype and 5xFAD mice"
17.	Abbi Hernandez, Caesar Hernandez, Leah Truckenbrod, Keila Campos, Quinten Federico, Jennifer L. Bizon, Sara N. Burke "Advanced age and ketogenic diet have dissociable effects across hippocampal subregions"
18.	Mary K Herrick, Madelyn C Houser, Cody E Keating, Lindsey Sniffen, Jianjun Chang, Malú G Tansey "LRRK2: Lurking between the brain and gut"
19.	Lucas James, Ariel Walker, Trey Polvadore, Malcolm Maden, Jada Lewis "The axolotl as a novel model of neurodegenerative disease and neuroresilience"
20.	Emily J Koller, Kristen R Ibanez, Elsa Gonzalez De La Cruz, Timothy Machula, Daniel Ryu, Benoit I Giasson, David R. Borchelt, Paramita Chakrabarty "Neuropathological outcomes in a mouse model of amyloid β and tau"
21.	Ashok Kumar, Jolie Barter, Asha Rani, and Thomas C. Foster Does systemic inflammation contribute to the senescent synapse?
22.	Katelyn N. Lubke, Sean M. Turner, Luis M. Colon-Perez, Marcelo Febo, Sara N. Burke "Aberrant response based strategies in old age are related to elevated *Arc* expression in the Dorsal Striatum"
23.	Fulvio R Mendes, Jenna L Leclerc, Lei Liu, Pradip Kamat, Damian Hernandez, Arash Naziripour, Abdullah S Ahmad, Sylvain Dore "Role of PGE2 EP1 receptor antagonist on stroke outcomes in Alzheimer Disease mouse models"
24.	Asha Rani, B. Yegla, J. Barter, A. Kumar, M. Febo, K. Esser, and T. C. Foster "Longitudinal characterization of sex differences in functional and cognitive decline during aging"

25.	Puja Sinha, Ashok Kumar, Asha Rani, and Thomas C. Foster "Effect of age and estrogen on whole genome DNA methylome profiling of CpGs in CA 1 region of the hippocampus.
26.	Garrett Smith, Asha Rani, Ashok Kumar, and Thomas Foster "Impaired Pattern Separation During Aging is Associated with Altered Hippocampal Gene Transcription"
27.	Ulm, Brittany Brittany Ulm, G. Xu, S. Fromholt, J. Howard, D. Borchelt, J. Lewis "Exacerbation of tauopathy in a mouse model of Alzheimer's disease"
28.	Ariel Walker, Sruti Rayaprolu, Jennifer Gass, John Howard, Lucas James, Colin Duffy, Jada Lewis "Progranulin deficiency causes early structural abnormalities in the periphery of knockout mice"
29.	Brittany Yegla, Esser, K., Foster, T.C. "Sex Differences in Exercise-induced Extracellular Vesicle Release and Cognitive Enhancement"
30.	Sabrina Zequeira, Sarah A. Johnson, Meena Ravi, Samm Smith, Andreina Hampton, Leslie S. Gaynor, Andrew P. Maurer, Jennifer L. Bizon, Sara N. Burke "Translational rat model of cognitive aging using a touchscreen operant platform to test visual discrimination and association"

University of Alabama at Birmingham

31.	Aundrea F. Bartley, Micah E. Bagley, Justin A. Barnes, David N. French, Timothy R. Totsch, Gary M. Gray, Lori L. McMahon and Lynn E. Dobrunz "Effects of X-irradiation on Neuronal and Circuit Function"
32.	Radhika Chadha and James H. Meador Woodruff "mTOR complex specific abnormalities in Schizophrenia brain"
33.	Rose B. Creed, Charlene Farmer, Rosalinda Roberts, Lori L. McMahon, Matthew S. Goldberg "Increased glutamatergic transmission at the corticostriatal synapse of PINK1 KO rats"
34.	Elizabeth S. Davis, Adam M. Goodman, Marc N. Elliott, Mark A. Schuster, Susan Tortolero Emory, Sylvie Mrug, David C. Knight "Violence exposure contributes to sex differences in the neural response to stress"
35.	Pinar Demirayak, Sara Sims, Utkarsh Pandey, Kristina M. Visscher **"**Primary visual cortex representing central, near peripheral, and peripheral vision are differentially functionally connected, and these differences follow patterns of known brain networks"
36.	Corey G. Duke, Jennifer J. Tuscher, Robert A. Phillips, Morgan E. Zipperly, Katherine E. Savell, Laura Ianov, & Jeremy J. Day "Dynamic gene expression in the nucleus accumbens following acute cocaine experience"

37.	Hyun Freeman, Jeff Killen, Roy C. Martin, Ismail S. Mohamed "Validation of a new computational approach for presurgical language lateralization in patients with refractory epilepsy"
38.	J.M. Froula, M. Castellana-Cruz, N. M. Anabtawl, J. Camino, S. Chen, D.R. Thrasher, J. Freire, A. A. Yazdi, S. Fleming, C. Dobson, J. Kumita, N. Cremades, L. Volpicelli-Daley, "Defining α-synuclein species responsible for Parkinson's disease phenotypes in mice"
39.	Shreya Malhotra, Gokulakrishna Banumurthy, Jada H. Vaden, Linda Overstreet-Wadiche, and Jacques I. Wadiche "Climbing fiber-mediated spillover transmission to interneurons is regulated by EAAT4"
40.	Kazuhito Nakao, Robert Hunter, Kiran Sapkota and Kazu Nakazawa "Glycogen synthase kinase 3 (GSK3) inhibition alleviates deficits in *in vivo* spike synchrony, gamma oscillation and cognitive impairment in a schizophrenia mouse model."
41.	Amani Norling, Marcas Bamman, Thomas Buford, Jonathan McConathy, Frank Skidmore, Virginia Wadley, Ronald M. Lazar "Cerebral Oxygen Perfusion and Exercise in Aging"
42.	Megan Rich, Eric Zhang, Katie Burdette, Ashley Dickey, Stephen Foulger, Kelli Cannon, Mark Bolding, "Noninvasive optogenetics using MRI-guided focused ultrasound delivery of radioluminescent nanoparticles"
43.	Jonathan R. Roth, Travis J. Rush, Samantha J. Thompson, Adam R. Aldaher, Jacob S. Mesina, J. Nicholas Cochran, and Erik D. Roberson "Tau-SH3 interactions are critical for amyloid-β toxicity in primary neurons"
44.	Mariangela Scarduzio, Karen L. Eskow Jaunarajs, Michelle E. Ehrlich, Lori L. McMahon, and David G. Standaert **"**Diverse mechanisms lead to common dysfunction of striatal cholinergic interneurons in distinct genetic mouse models of dystonia."
45.	Sims, Sara A., Pandey, Utkarsh, Cedotal, Simone, Robinson, Jennifer L., Visscher, Kristina M. "Retinotopic patterns of structural connectivity between V1 and functional networks"
46.	Nash Vador, Wei Li Ph.D., Lucas Pozzo-Miller Ph.D. Indirect Dopaminergic Fiber Modulation of Purkinje Cells Through Bergmann Glial Cells in Rett Syndrome Mice
47.	Yuliya Voskobiynyk, Jonathan Roth, J. Nicholas Cochran, Travis Rush, Kelsey Greathouse, Nancy Carullo, Lori McMahon, Jeremy Herskowitz, Jeremy Day, Erik D Roberson "The Alzheimer's Disease Risk Gene *BIN1* Regulates Neuronal Hyperexcitability"

University of Arizona

48.	Pradyumna Bharadwaj, Jessica Andrews-Hanna, Philip Kuo, Gene Alexander “Alzheimer's disease fluid biomarkers related gray matter covariance patterns in healthy older adults”
49.	Greg Branigan, Lucia Whitman, Mandi J. Corenblum, Lalitha Madhavan, Roberta Diaz Brinton “Comprehensive phenotyping of patient-derived fibroblasts from patients with sporadic Alzheimer’s Disease”
50.	Monica K. Chawla, Marc A. Zempare, Victor J. Hruby, Carol A. Barnes, Minying Ca “Age-related, specific changes in expression of several central melanocortin receptor subtypes in the rat”
51.	Mandi J. Corenblum, Anandhan Annadurai, Kanchan Shrestha, Lalitha Madhavan **“**A patient iPSC-based platform for investigating idiopathic Parkinson’s disease”
52.	Lindsey M. Crown, Daniel T. Gray, Lesley A. Schimanski, Carol A. Barnes, Stephen L Cowen “Spatial eye-blink learning but not age predicts theta-gamma coupling in the CA1 region of the hippocampus”
53.	Randall Eck, Monica K. Chawla, Bhavani Bagevalu Siddegowda, Natalie J. Carey, Marc A. Zempare, Christie J. Nguyen, Dean Billheimer, Carol A. Barnes, Daniela C. Zarnescu “RNA stress granule components are dynamically expressed during aging and stress conditions in rats and fruit flies”
54.	Daniel T. Gray, Wonn Pyon, Nicole De La Peña, Rachel Schwyhart, Emma Wallace, Joana Puchta, Wolfgang Härtig, Carol A Barnes “Perineuronal nets in the cerebral cortex of cognitively-assessed aged macaque monkey”
55.	Adam W. Lester, Adele J. Kapellusch, Carol A. Barnes “A computational model of aged head direction network updating in the presence of sudden spatial cue mismatch”
56.	Stephanie Matijevic, Max Elias, Matthew J Huentelman, Lee Ryan “Interactive effects of sex and BDNF Val66Met polymorphism on cognition in older adults”
57.	Aarti Mishra, Yuan Shang, Yiwei Wang, Fei Yin, Roberta Diaz Brinton “The immuno‐metabolic crisis in the aging female brain: Implications for Alzheimer's disease”
58.	Justin M Palmer, Ashley V Lawrence, Matthew D Grilli, Matthew J Huentelman, Joshua S Talboom, Lee Ryan “Context-dependent memory in cognitively-normal older e4 carriers and non-carriers”
59.	Wonn S. Pyon, Daniel T. Gray, Rachel E. Schwyhart, Emma G. Wallace, Nicole de la Peña, Carol A. Barnes “Quantification of neuronal and astrocytic cells in the locus coeruleus of

	cognitively assessed, young and aged nonhuman primates”
60.	Sahana V. Srivathsa, Salma O. Khattab, Adam W. Lester, Carol A. Barnes “Role of prefrontal-hippocampal interactions in age-related deficits in spatial working memory”
61.	Joshua S Talboom, Asta K Håberg, Matthew D. DeBoth, Marcus A Naymik, Isabelle Schrauwen, Candace R Lewis, Ashley L Siniard, Stacy F Bertinelli, Callie Hammersland, Amanda J Myers, Meredith Hay, Carol A Barnes, Elizabeth Glisky, Lee Ryan, Matthew D Huentelman “Web-based study of forty-one thousand women reveals factors associated to cognitive enhancement during menopause”
62.	Emily Van Etten, Pradyumna Bharadwaj, Georg Hishaw, Theodore Trouard, Gene Alexander “Mediation of age and hippocampal volume by temporal lobe white matter hyperintensities differ in relation to APOE e4 status in healthy older adults.”
63.	Yiwei Wang, Yuan Shang, Aarti Mishra, Eliza Bacon, Fei Yin, Roberta Diaz Brinton “Dynamic metabolic aging of the female brain during endocrinological and chronological aging”
64.	Marc Zempare, Natalie J. Carey, Amy Dalmendray, Kimberly Young, Kimberly M. Bohne, Loi Do, Theodore Trouard, Kenneth D. Mitchell, Monica K. Chawla, Matthew J. Huentelman, Carol A. Barnes “Effects of induced hypertension in middle aged CYP1A1-REN2 transgenic rats”

Inter-Institution

65.	Authors: This is a team effort by the McKnight Brain Aging Registry Investigators and Collaborators “Characterizing the Healthy Oldest Old: The McKnight Brain Aging Registry” Institutions: Evelyn F McKnight Brain Institute, University of Alabama, Birmingham; Evelyn F. McKnight Brain Institute, University of Arizona; Evelyn F. McKnight Brain Institute, University of Florida; Evelyn F. McKnight Brain Institute, University of Miami
66.	Eric Porges, Jensen G, Bharadwaj PK, Franchetti MK, Sims SA, Rezaei RF, Forbes MA, Merritt S, Jessup CJ, Raichlen DA, Geldmacher D, Hishaw GA, Alperin N, Trouard TP, Wadley VG, Levin BE, Woods AJ, Rundek T, Visscher KM, Cohen RA, Alexander GE, Foster BM, Puts NAJ “Age related decreases in cortical GABA concentrations assessed over the lifespan abate in cognitively intact adults over 85 years of age”
67.	David Raichlen, Pradyumna Bharadwaj, Mary Franchetti, Sara Sims, Roxanne Rezaei, Suzanne Merritt, Cortney Jessup, Eric Porges, David Geldmacher, Georg Hishaw, Noam Alperin, Theodore Trouard, Virginia Wadley, Bonnie Levin, Adam Woods, Tatjana Rundek, Kristina Visscher, Ronald Cohen, Gene Alexander

	"Relation of daily activity patterns to cortical gray matter maps in the healthy oldest old: Findings from the McKnight Brain Aging Registry."
68.	Kristina Visscher, Paul Stewart, Sara Sims, Bharadwaj PK, Franchetti MK, Rezaei RF, Merritt S, Jessup CJ, Raichlen DA, Eric Porges, David Geldmacher, Hishaw GA, Noam Alperin, Trouard TP[5], Virginia Wadley, Bonnie Levin, Adam Woods, Tanji Rundek, Ron Cohen, Gene Alexander "Functional connectivity in the healthy oldest old: Findings from the McKnight Brain Aging Registry"

MBRF Sponsored Abstracts at the 2019 Society for Neuroscience Conference

Ralph Sacco, M.D.
Executive Director

Tatjana Rundek, M.D., Ph.D.
Scientific Director
Evelyn F. McKnight Chair for Learning and Memory in Aging

Poster 1

Exercise Barriers, Motivators, and Self-efficacy in Sedentary Aging Adults: An Ongoing Trial

Danylo Cabral, Jordyn Rice, Christina Nunez, Danielle Abel, Kaylee Van Deusen, Baabak Moustafi, Marcela Kitaigorodsky, David Loewenstein, Lawrence Cahalin, Tatjana Rundek, Joyce Gomes-Osman

Abstract:

Purpose/Hypothesis: Only one in three adults meet the recommended weekly minutes of physical activity. Despite the strong evidence supporting a multitude of positive health outcomes from being physically active (including improved cognition), it is of utmost importance to increase physical activity in our aging population. A greater understanding of the barriers and motivators to exercise in aging adults would help to facilitate increasing physical activity in a population specific manner. Additionally, physical activity levels vary across geographical regions within the United States, and therefore, there may be region specific barriers and motivators to exercise. Furthermore, self-efficacy (believing that one is capable of carrying out a course of action) is related to motivation and persistence, and thus, may be an important factor in better understanding factors that promote exercise adherence in aging adults. Given the importance of creating individualized exercise recommendations to increase physical activity in aging adults, we aimed to explore the effect of a supervised aerobic exercise intervention in modifying attitudes towards exercise barriers, motivators and self-efficacy in sedentary aging individuals.

Methods: Currently nineteen ($\geq$55 years and old; mean age=60.6$\pm$3.9; 56.5% females; 56.5% Hispanic) cognitively healthy (MoCA $\geq$ 24; mean=25.4) individuals completed the baseline assessment and nine have completed the study. At baseline and post aerobic exercise intervention (60 min daily sessions of, 3x/week for 8 weeks) participants completed questionnaire of barriers to physical activity and exercise (15 items), motivators to be physically active (6 items). Self-efficacy was measured with a 9-item scored questionnaire, with higher scores indicating poorer self-efficacy (score range=9-36 points)

Results: At baseline, 74% of participants reported being insufficiently active. The most commonly cited barrier was the lack of company, or a group to exercise (58%). Other barriers included lack of accountability, lack of motivation, and poor health. In counterpart, access to facilities (92%), accessibility and safety (85%) represented the most commonly cited motivators. Other motivators included: improvements in health condition, accountability, financial compensation, education, and appearance. Only 38.89% reported 'very sure' to exercise 3x/week for 20 minutes. In situations such as tiredness, under pressure, down or depressed, too much work at home, more interesting things to do, no support from friends and family, and when they don't like it, more than 50% (50 to 72% range) answered they were "not all sure" they would exercise regularly. A pre to post analysis showed a positive change towards increase in self-efficacy (change mean= -11, p=.40).

Conclusion: An 8-week supervised aerobic exercise intervention was able to positively change attitudes towards self-efficacy in a cognitively health adult population. These findings highlight specific barriers and motivators that can be intervened to promote changes in physical activity in aging adults. Future studies should also consider a health education component including self-regulation to promote long-lasting changes and adherence to exercise.

Poster 2

Effects of 8-weeks of Aerobic Exercise Intervention on Fitness and Neuroplasticity in Aging Adults: Preliminary Results of an Ongoing Trial

Danylo Cabral, Jordyn Rice, Christina Nunez, Danielle Abel, Kaylee Van Deusen, Baabak Moustafi, Marcela Kitaigorodsky, David Loewenstein, Lawrence Cahalin, Tatjana Rundek, Joyce Gomes-Osman

Abstract:

Purpose/Hypothesis: Aerobic exercise is known to promote cognitive brain health in aging adults, but the exact mechanisms are not fully elucidated. Studies in animal models and humans have attributed exercise-mediated cognitive improvements to two main mechanisms: neuroplastic changes in the nervous system measured by enhanced synaptic activity; and increased cardiovascular fitness, which would mediate local increased blood flow, release of trophic factors and promote structural changes. We aimed to assess both neuroplasticity and cardiovascular fitness in sedentary aging individuals who participated in an 8-week progressive exercise intervention. We hypothesized that neuroplasticity and cardiovascular fitness would improve from pre to post-intervention, and that there would be a positive relationship between the two.

Methods: Nine (≥55 years old; mean age=60.6±3.9; 55.6% females; 56.5% Hispanic) cognitively healthy, (MoCA ≥ 24; mean=26.1) sedentary individuals have completed the intervention. Participants engaged in a supervised aerobic exercise intervention 3x/week over the course of 8 weeks for a total of 24 exercise visits. Exercise sessions were 60 minutes of steady-state aerobic exercise on either a treadmill, elliptical, or bike, delivered at moderate intensity (55-64% Karvonen equation) for the first 4 weeks and high intensity (65%-90% Karvonen equation) for the last 4 weeks. At baseline and post-intervention, participants performed a neuroplasticity assessment utilizing transcranial magnetic stimulation (TMS), and an Incremental Shuttle Walking Test (ISWT) to assess cardiovascular fitness. The neuroplasticity assessment consisted of measuring the amplitude of motor evoked potentials (MEPs) at baseline (T0) and following intermittent theta-burst stimulation (iTBS), at regular intervals (T5, T10, T20, T30). The neuroplasticity measure consists of quantifying iTBS-induced modulation of MEPs at T5 and T10. The cardiovascular fitness measures derived from the ISWT were maximal walking velocity and walking distance, which were used to predict VO2 peak as a measure of aerobic capacity. Heart rate recovery (HRR) value was defined as the change in the heart rate from the peak of exercise to the heart rate after 1-min and 2-min cessation.

Results: There were trends toward significant increases of 40.93% in the percent change MEP from baseline to post iTBS at T5 (p=.065). A significant pre to post increase in HRR at 1-min (p=.011) and 2-min (p=.007) was found. There were no significant changes in VO2 peak. In addition, a significant correlation between percent change after iTBS and HRR at 1-min after the ISWT were found at T5 (p=0.013, r=.624) and T10 (p=.008, r=.636) at baseline.

Conclusion: In this preliminary and ongoing trial, an 8-week progressive aerobic exercise intervention demonstrated increased neuroplasticity utilizing a TMS iTBS assessment. Early patterns in the data suggest that while there was an increase in neuroplasticity from pre to post intervention this was not associated with increased cardiovascular fitness as measured by the ISWT. As the study progresses, an increased sample size will improve statistical power and allow further analyses to be conducted.

Poster 3

Red blood cell-derived microparticles treatment improves post-intracerebral hemorrhage in long-term outcomes in rats.

Sunjoo Cho, Ashish K. Rehni, Hever Navarro Quero, Carolyn J. Keatley, Shyam Gajavelli, Sebastian Koch, Yeon S. Ahn, Miguel A. Perez-Pinzon, Wenche Jy, Kunjan R. Dave

Abstract:
As spontaneous intracerebral hemorrhage (sICH) is the deadliest stroke sub-type with no therapeutic options, the prevention of hematoma expansion is a potential therapeutic target. Our earlier studies showed that treatment with red blood cell-derived microparticles (RMP), a hemostatic agent[1], lowered post-sICH hematoma volume 24 h post-collagenase injection. The goal of this study was to evaluate the potential of RMP therapy in improving primary and secondary long-term outcomes in a rat model of sICH. RMPs were prepared from human RBCs[1]. sICH was induced in young Sprague-Dawley male rats by injecting collagenase into the right striatum. Rats were randomly assigned to vehicle, RMP ($2.55x10^{10}$ particles/kg, b.w. i.v.), or recombinant Factor VIIa (rFVIIa) (positive control, 120 µg/kg, b.w. i.v.) treatment groups. RMP dose and treatment paradigms were determined based on earlier pharmacokinetic, dose response, and multiple paradigm comparison studies. On day 28 post-sICH, rats were euthanized to collect brains for histological assessment. In an earlier study to be presented at the Brain 2019 conference, we reported that both RMP- and rFVIIa-treatments significantly lowered neurological deficit scores than the control group up to 14 days post-sICH. We also reported that in the ladder rung walking test when compared to the baseline, the control group had a significantly greater percentage of contralateral foot faults up to 28 days post-sICH, and the rFVIIa group had significantly greater foot faults up to 21 days post-sICH. However, the RMP group did not have foot faults significantly different than the baseline at any time point. We next evaluated brain histopathology, focusing on bregma levels +3.0 to -3.0. Animals with more than 2 sections missing at the level of interest (6 animals) and improper injection location (4 animals) were excluded from the analysis. The RMP-treated group was compared with the control and rFVIIa-treated groups using Student's t-test. Based on our results so far, we observed that the damaged brain volume was significantly lower in the RMP group (n=11) than the control ($p<0.05$, n=9) and rFVIIa ($p<0.05$, n=12) groups by 28% and 29%, respectively. We are in the process of evaluating histopathology of the remaining animals belonging to all experimental groups. Our results indicate that RMPs have the potential to not only lower hematoma growth, but also improve long-term outcomes post-sICH.

References: 1) Thrombosis and Haemostasis. 2013;110(4):751-60. Grant support: NIH/NS094896. Conflict of interest: RxMP Therapeutics provided the testing material for the study. Dr. Ahn, Dr. Jy, and the University of Miami have partial ownership in RxMP Therapeutics. Drs. Ahn and Jy are the inventors of 2 US patents related to red cell microparticles. Drs. Ahn and Jy also received grant support from RxMP Therapeutics.

Poster 4

Ethnicity moderates the relationship between sleep quality and learning and memory.

Crespo, Krizia, Kaur, Sonya, McInerney, Katalina, Rooks, Joshua, Sarno, Marina, Slugh, Mitchell, Getz, Sarah, Bure-Reyes, Annelly, Banerjee, Nikhil, Rundek, Tatjana, Levin, Bonnie

Background/Objectives: Cognition is an important predictor of functional independence and quality of life in older adults. Poor sleep quality is a strong contributor to cognitive decline. There is a growing body of evidence suggesting Hispanic/Latinx (H/L) may differ from non-H/L individuals in sleep characteristics. The current study examined whether the relationship between sleep quality and cognitive dysfunction was moderated by ethnicity in a sample of non-demented older adults.

Subjects/Methods: Two hundred fifty three participants (119 H/L), ranging in age from 50-92 years (M= 67.59 years, S.D.= 9.22 years) were recruited from the McKnight Brain Research Registry at the University of Miami School of Medicine. All participants underwent a neuropsychological evaluation and completed a self-report sleep questionnaire. Direct effects of sleep quality on cognitive domains and statistical moderation were assessed using nonparametric bootstrapping.

Results: Poor sleep quality predicted poorer performance on learning (β= -0.05), delayed recall (β= -0.06) and processing speed (β= -0.03). The relationship between sleep quality and memory was significantly moderated by ethnicity (β= 0.06, B= 0.08), where there was a significant relationship between sleep quality and learning (β= -0.05) as well as delayed recall (β= -0.06) in non H/L participants but not in H/L participants (β= 0.02 & β= 0.02). There were no significant differences in sleep quality (t= -0.47) and learning and delayed recall between ethnic groups (t= 1.21 & t = 1.03).

Conclusions: The relationships between sleep quality and measures of learning and memory were statistically moderated by ethnicity. These differences are not explained by ethnic differences in overall sleep quality or baseline differences in memory. This is consistent with the literature emphasizing differential effects of risk/lifestyle factors on cognition among H/L participants. It is possible that the relationship between sleep quality and cognition in H/L participants is altered by additional cultural or genetic factors and warrant further investigation.

Poster 5

Fatigue, Adverse Childhood Experiences, and Frailty in Later Life

Sarah J. Getz, Joshua Rooks, Katalina F. McInerney, Nikhil S. Banerjee, Bonnie E. Levin

Abstract:
Objectives: Exposure to adverse events in childhood has been associated with negative health outcomes across the life span. The Fried Frailty phenotype, the most widely employed criteria to define frailty, consists of a collection of five symptoms signifying a generalized diminution in physiologic reserve and depleted resistance to stressors which include unintentional weight loss, self-reported fatigue/exhaustion, weakness, reduced gait speed, and low physical activity. Measurements: The current study used the Fried criteria to examine whether adverse childhood events are selectively linked to one or more of the five symptoms. Results: A linear regression, controlling for age, education, depression, anxiety, ethnicity, and community vs. clinic participant showed that adverse childhood events significantly predicted the number of frailty symptoms in a population of adults age 65 and older. Subsequent logistic regressions examining adverse childhood events and individual frailty symptoms indicated that fatigue was uniquely associated with childhood trauma, whereas the relationship between adverse childhood events and other frailty symptoms was non-significant. Conclusions: These findings add to the growing literature showing that early life stress is associated with negative health outcomes older age. Specifically, self-reported fatigue in the context of the frailty syndrome in middle and later life may be best viewed for select individuals from a developmental perspective that takes into account the long-range impact of childhood trauma.

Poster 6

Chronic nicotine exposure hinders whole body vibration therapy induced ischemic protection in the brain of reproductively senescent female rats

Ami P. Raval, William Javier Moreno, Juliana Sanchez, Nadine Kerr, Ofelia E. Furones-Alonso, W. Dalton Dietrich, Helen M. Bramlett

Abstract:
Stroke disproportionately kills more women than men and the risk of stroke remains high even at a young age among women smokers. Smoking prior to stroke is associated with increased post-stroke frailty. Frailty is characterized by an increased vulnerability to acute stressors and the reduced capacity of various bodily systems due to age-associated physiological deterioration. Such age related physiological deterioration of bone in laboratory animals and humans has shown to reverse after therapeutic intervention of whole body vibration (WBV) (*1*). Our recently published study shows that post-stroke WBV intervention reduces ischemic brain damage in reproductively senescent female rats (*2*), suggesting WBV may be a potential therapy to reduce post-ischemic frailty and improve functional and cognitive outcomes after stroke. In the current study we aim to test the efficacy of WBV in reducing post-ischemic frailty and improving physical activity and cognition using a rat model of smoking attributed nicotine. Nicotine or saline exposed adult female rats underwent transient middle cerebral artery occlusion (tMCAO; 90 min) / sham-surgery and randomly assigned (n = 6-8 per group) to either WBV or control groups. Animals placed in the WBV (40 Hz) group underwent 30 days of WBV treatment performed twice daily for 15 min each session for 5 days each week. We monitored the frailty index (FI) prior to and 1 month after tMCAO alone or in combination with WBV. The FI was composed of the following criteria: 1) activity levels, 2) blood pressure (BP), 3) basic metabolic status, and 4) cognitive performance of rats. Animals were sacrificed on the 30th day of WBV treatment, and brain tissue was harvested for histopathological analysis. Post-tMCAO WBV did not change activity levels or BP in nicotine or saline treated rats. Post-tMCAO WBV cognitive performance improved in saline group as compared to nicotine exposed rats. Sensorimotor function was also improved in tMCAO WBV saline group compared to nicotine-exposed rats. We observed 56% reduction in infarct volume of WBV treated rats as compared to control ($p < 0.05$). This difference was not seen in nicotine treated groups. The post-ischemic WBV intervention had no detrimental effects on the frailty parameters, decreased brain damage, and reduced frailty in control female rats, but not in the nicotine-exposed group. This suggests that WBV may be a potential therapy for non-smokers to reduce post-ischemic frailty and improve functional and cognitive outcomes after stroke.

Reference:
1. H. M. Bramlett *et al.*, *Osteoporosis international* **25**, 2209-2219 (2014).
2. A. P. Raval *et al.*, *Int J Mol Sci* **19**, (2018).

Poster 7

Effects of endogenous estrogen fluctuations on the post-ischemic innate inflammation in the brain of female rats.

Varun Reddy, Concepcion Furones, Juan Pablo de Rivero Vaccari, Ami Raval

Abstract:
One out of five women suffer stroke after menopause in the United States. Menopause is characterized by decline in endogenous estradiol-17 beta (E2). Estrogen is neuroprotective against ischemia; however, concern regarding the safety of E2 therapy in menopausal women has prohibited translation of this phenomenon to the clinic. In spite of these findings, women appear to be naturally protected against ischemic neuronal damage during pre-menopausal life, suggesting some estrogen-influenced neuroprotective mechanism. Thus, a better understanding of the cellular and molecular mechanisms by which endogenous estrogen fluctuations govern the female brain is required. In a recent study, we presented data suggesting a key role of estrogen in regulation of inflammasome activation in the female rat brain. Inflammasome is a multiple protein complex and is the main component of innate immune response. The aim of current study is to test effects of higher and lower levels of endogenous E2 on post-stroke inflammasome proteins. We hypothesized that prevailing higher levels of endogenous E2 during estrus would protect the brain from ischemic injury by reducing inflammasome activation. The proposed hypothesis was tested using young female (4-6 months), retired breeder (9-13 months), and age-matched male Sprague-Dawley rats. Rats were randomly exposed to transient middle cerebral artery occlusion (tMCAO; 90 min) or sham surgery. Twenty-four hours after tMCAO, brains were removed rapidly and sectioned into 1 mm slices beginning from the rostral end, and the area of infarction was visualized by incubating the sections in 1.5% TTC (2,3,5-triphenyltetrazolium chloride; Sigma Aldrich) in PBS for 15mins at 37°C. The infarct volume was measured using ImageJ software. In a separated cohort of rats, brain tissue was collected for western blot analysis 24h after tMCAO/sham surgeries. We observed significantly ($p<0.05$) reduced infarct volume in young female rats, which underwent tMCAO during estrus stage (higher levels endogenous E2) as compared to diestrus (lower levels of circulating E2). Results also showed that the brain of young rats had significantly lower infarct volume and reduced inflammasome activation in the brain as compared to reproductively senescent female rats. Our study demonstrated that endogenous E2 regulates innate immune response in the brain of female rats.

Poster 8

Prior exposure to recurrent hypoglycemia causes post-ischemic ER stress via increased free radical production in treated diabetic rats.

Ashish K. Rehni, Sunjoo Cho, Kunjan R. Dave

Abstract:
Cerebral ischemia is a serious complication of diabetes. Antidiabetic drugs induce recurrent hypoglycemia (RH). Previously, we showed that prior RH exposure enhances ischemic brain damage in insulin-treated diabetic (ITD) rats. However, the mechanism of this increase in ischemic injury is unknown. In the present study, we evaluated the hypothesis that enhanced acidosis causes an increase in free radical release, resulting in endoplasmic reticulum (ER) stress. Previously, we showed that the administration of an alkalizing agent (Tris-(hydroxymethyl)-aminomethane: THAM) decreases intra-ischemic acidosis in RH-exposed ITD (ITD + RH) rats. As acidosis increases the levels of free radicals, we determined that the administration of THAM decreases RH-induced post-ischemic increase in hydrogen peroxide production and microsomal calcium release in ITD + RH rats. Male Wistar rats were rendered diabetic by streptozotocin and, 2-3 weeks later, insulin pellets were implanted to treat hyperglycemia. After 1-2 weeks, moderate hypoglycemia was elicited by dose(s) of insulin for 3 hours for 5 consecutive days. The following groups were employed: (A) ITD + vehicle (Veh) (n = 7): (B) ITD + RH + veh (n = 7) and, (C) ITD + RH + THAM (0.3 M, 3 ml / kg / hr, i.v.) (n = 7). Global cerebral ischemia (by bilateral carotid artery occlusion with hypotension) was induced for a period of eight minutes overnight after the last episode of hypoglycemia/equivalent time. THAM/Veh treatment was given 15 min before ischemia to 80 minutes of reperfusion. Hippocampii were harvested 23-25 h after ischemia. We measured the rate of hydrogen peroxide production in the homogenate using the Amplex Red fluorometric assay and microsomal calcium release. The rate of H_2O_2 production in ITD + RH rats 24 h after ischemia (128 ± 12 AFU/min/mg protein) was significantly higher (58%; $p<0.01$) than that of the ITD control group (81 ± 9 AFU/min/mg protein). The rate of H_2O_2 production in THAM-treated rats (81 ± 11 AFU/min/mg protein) was significantly lower (37%; $p<0.05$) than that of the RH + ITD + Veh control group. However, we did not observe any significant difference between ITD and ITD + RH + THAM groups. We are in the process of determining calcium release in microsomes. Our results, so far, demonstrate that ischemic acidosis increases the rate of H_2O_2 production in ITD + RH rats. Given the lack of understanding of the role played by hypoglycemia in mediating diabetic aggravation of ischemic brain injury, elucidating the mechanism of ischemic damage in RH-exposed ITD rats will help in identifying new therapeutic strategies to treat the serious condition in diabetics.

Poster 9

Measuring Frailty in Middle and Later Years and its Association with Cognition

Rooks J., Banerjee, N., Goodman, Z., McInerney, K. F., Getz, S., Kaur, S., and Levin, B. E.

Objective: 1) Assess whether a latent measurement of Frailty (Fried et al., 2001) is invariant across middle-aged and older adults 2) Examine age-related differences in the Frailty-cognition link.

Participants and Methods: 361 adults (M_{age} = 67.8 years, range: 45-92; 63.7% female) without primary neurological disorders were recruited from University of Miami clinics and surrounding community centers. Participants completed neuropsychological and frailty (grip-strength, gait speed, physical activity, weight-loss, fatigue) assessments. First, we ran a confirmatory factor analysis (CFA) of the Frailty factor, indicated by five continuous measures of frailty symptoms. Second, measurement invariance (MI) was tested between middle/young older (<65 years; n = 125) and older (≥65 years; n = 236) adults. Third, we analyzed the effects of frailty on five cognitive domains (language, visuospatial, memory, processing speed & executive functioning) as well as a Generalized Cognition factor (with all five domains as loadings), controlling for demographic, psychological (including depression), and medical covariates. Finally, we tested age-group as a moderator.

Results: For the Frailty CFA, weight loss was the only indicator that did not load, and therefore was removed. Results indicated the relationship between the frailty indicators were comparable in both age groups, however, the intercept of fatigue was disproportionately higher among the middle/young older cohort, leading to misfit in the scalar model. Frailty was inversely associated with all cognitive domains. This effect did not differ between groups.

Conclusion: Results largely support the construct validity of frailty among both middle/young older and older adult cohorts but raise questions about the inclusion of weight loss as a core symptom. A novel finding is that fatigue was found to be a particularly salient feature of frailty in the middle/young old years and may play an especially important role in how frailty is defined in this subgroup. This study also demonstrated that frailty is associated with poorer overall cognition for both age groups and not unique to older adults. These data support prior research showing the importance of studying frailty and functional changes in the middle years with fatigue as a particularly prominent feature that is not necessarily associated with depression. Further research examining the role of fatigue in middle years and its association with cognition over time may provide unique insights on how to intervene earlier in the life course before functional decline begins.

Poster 10

Post-stroke physical exercise reduces ischemic brain damage and improves cognition in reproductively senescent female rats

Sharnikha Saravanan, Concepcion C Furones, Weizhao Zhao, Kunjan R Dave, Miguel A Perez-Pinzon, Ami P Raval

Abstract:
Stroke disproportionately kills more women than men and even a mild stroke causes disability in post-menopausal women. Menopause is defined as the menstrual cycle ceases due to anovulation. Notably, menopause is not an abrupt event. The overall process of menopause lasts for years and during that period, disruption of multiple estrogen-regulated systems and domains of cognitive function can be affected. Cognitive decline is a significant consequence of stroke survivors and two-thirds of stroke survivors experience cognitive deficits that last at least up to 6 years post-stroke. Our earlier study demonstrated that physical exercise (PE) reduced post-stroke brain injury and improved cognitive functions in male rats. However, efficacy of PE in female counterparts remains elusive and the focus of our current study is to evaluate the improvement of post-stroke cognitive function in female rats. Reproductively senescent Sprague–Dawley female rats were exposed to transient middle cerebral artery occlusion (tMCAO; 90 min) and randomly assigned to either PE or sham-PE groups. After three to five days, rats underwent sham-PE (0m/min speed) or PE (15m/min speed) for 30 mins either every day or alternate day for five times on treadmill. The rats that underwent alternate day paradigm were treated with ER-β agonist (beta 2, 3-bis(4-hydroxyphenyl) propionitrile; DPN; 1mg/kg) or vehicle-DMSO immediately following PE/sham-PE session to determine the synergistic effect with physical exercise since ER-βagonist is shown to reduce ischemic damage. Seven days after the last PE/sham-PE, rats were tested for hippocampal-dependent contextual fear conditioning and freeze time was measured. Following behavioral testing, rats' brains were processed for histology and infarcted area was measured using MCID software. Results demonstrated that post-tMCAO continuous PE did not reduce ischemic damage. However, alternate PE regimen with or without ER-β agonist reduced infract volume by 20% and 23%, respectively. Similarly, alternate PE regimen showed increased freezing on the second day of fear conditioning by 15%, indicating improved spatial memory. Overall, the study suggests that an alternate day PE paradigm and ER-β activation improves post-stroke cognition and future studies delineating underlying mechanism could help identify therapies to prevent/reduce stroke related cognitive decline in menopausal women stroke patients.

Todd Golde, M.D., Ph.D.
Executive Director

Steven DeKosky, M.D.
Deputy Director

Tom Foster, Ph.D.
Evelyn F. McKnight Chair for Research in Cognitive Aging and Memory

Ronald Cohen, Ph.D.
Evelyn F. McKnight Chair for Clinical Translational Research in Cognitive Aging and Memory

Poster 11

Age and Sex Influence the Hippocampal Response and Recovery Following Sepsis

Jolie Barter, Ashok Kumar, Julie A. Stortz, McKenzie Hollen, Dina Nacionales, Philip A. Efron, Lyle L. Moldawer, and Thomas C. Foster

Abstract:
Although in-hospital mortality rates for sepsis have decreased, survivors often experience lasting physical and cognitive deficits. Sex and age are major factors contributing to variability in the response to sepsis. Many studies in humans and rodents have demonstrated decreased mortality following sepsis for females and the incidence of sepsis and associated complications increase with advancing age. We employed a murine model to examine the influence of age and sex on the brain's response and recovery following sepsis. Young (~4 months) and old (~20 months) mice (C57BL/6) of both sexes underwent cecal ligation and puncture (CLP) with restraint stress. The hippocampal transcriptome was examined in age and sex-matched controls at 1 and 4 days post-CLP. A considerable number of hippocampal genes were altered in a similar manner across all sex and age groups on day 1. In general, immune and stress-related genes increased while neuronal, synaptic, and glial genes decreased one day after CLP-induced sepsis. However, specific age and sex differences were observed for the initial responsiveness to sepsis as well as the rate of recovery examined on day 4. Young males differentially expressed a substantial number of genes 1 day after sepsis, but recovered normal gene expression profile 4 days after sepsis. Young females were the least responsive group across the four days of sepsis, exhibiting the fewest number of altered genes and gene ontology clusters. Old females exhibited a robust shift in gene transcription on day 1 and, while most genes recovered, genes linked to neurogenesis and myelination continued to be downregulated by day 4. In contrast, old males exhibited a more delayed or prolonged response to sepsis, such that neuronal and synaptic genes continued to decrease while immune response genes continued to increase on day 4. The genes that were altered on day 4 in older animals may shed light on the mechanism for sepsis-induced cognitive impairment, which is particularly evident in older individuals. These results suggest that aging is associated with delayed recovery from sepsis, which is particularly evident in males.

Poster 12

Regulation of risky decision making via activity in dopaminergic neurons in the ventral tegmental area.

Blaes, S.L., Orsini, C.A., Holik, H.M., Wilson, J., Singhal, S.M., Frazier, C.J., Bizon, J.L., Setlow, B.

Abstract:
The ability to decide adaptively between options associated with different rewards and risks is critical for well-being and quality of life, and impairments in this form of decision making are associated with a range of psychiatric disorders. Dopamine signaling plays a critical role in such "risky" decision making, but the contributions of dopaminergic activity to temporally-discrete components of the decision process is not well understood. To address this issue, an optogenetic approach was used to inactivate dopaminergic neuron cell bodies in the ventral tegmental area (VTA) in rats during performance of a risky decision-making task. Verification experiments indicate robust selectivity of transgene (mCherry) expression for TH+ neurons, and that 560 nm light is effective in silencing spiking activity in transduced neurons in midbrain slice preparations. Male and female tyrosine hydroxylase-cre rats underwent surgery to inject AAV- EF1a-DIO-eNpHR3.0-mcherry (which carries the gene for halorhodopsin) into the VTA, followed by implantation of an optic fiber targeting the VTA. Rats were then trained in a task in which they made discrete trial choices between a small, "safe" food reward and a large, "risky" food reward accompanied by varying probabilities of footshock punishment as in Orsini et al. (2017). Once stable task performance was achieved, the VTA was optogenetically inactivated during discrete task epochs, including deliberation (prior to choices) and during delivery of the various choice outcomes. Initial data suggest that inactivating VTA dopaminergic neurons during receipt of the large, unpunished reward reduces rats' preference for the risky option (i.e., decreases risky choice). These results are consistent with the idea that brief reductions in tonic dopaminergic neuron activity signal negative reward prediction errors regarding the outcomes of behavior, rendering the actions that led to those outcomes less attractive during subsequent choices. Ongoing experiments are testing effects of VTA inactivation in other task epochs, as well as effects of VTA activation via channelrhodopsin.

Poster 13

A potential experimental therapy for TBI-induced disabilities in a rodent model

P. Bose, J. Hou, S. Tsuda, R. Nelson, D. Plant, R. J. Bergeron, F. J. Thompson

Abstract:
There is a need to increase our understanding of TBI-induced long-term disability mechanisms, and to test the safety and efficacy of therapeutic measures that target these mechanisms utilizing approaches that have excellent potential for rapid translation. Acceleration/deceleration closed head traumatic brain injury (CH-TBI) induces damage of micro-vessels which results in endothelial shear injury, blood brain barrier (BBB) dysfunction, and micro-bleeding. Microbleed-derived iron can provide an enduring inflammation, further breakdown of the BBB tight junctions, and cell death through multiple inflammatory pathways. Thus, removal of toxic iron is potentially an important therapeutic design for TBI treatment and rehabilitation. Thus, the current studies tested the influence of injury and compared the therapeutic impact of 2 iron chelators on hallmark disabilities in a rodent model of CH-TBI. Mild/moderate CH-TBI was produced using our previously reported protocol (450 g/1.25m). NaHBED (n=10) and Deferoxamine (DFO; n=5) treatments were initiated PO Day-0 and continued through PO Wk-2 (50 mg/kg/day for 2 wks, SQ). The control animals received equal volume of saline (SQ; n=7). The outcome measures for spasticity, balance, gait, anxiety and cognitive functions were compared in the saline control and 2 iron chelators treated groups. Our data to date revealed long-term disabilities in motor/vestibulomotor, anxiety and cognitive behaviors following CH-TBI, and significant reductions in these disabilities by NaHBED treatment. By comparison, the DFO treatment was less effective in reducing spasticity. This difference in treatment efficacy might be due to the comparatively lower iron clearing potency of DFO. Immunohistochemistry studies of TBI tissues showed patterns of a) iron deposition and disruption of BBB, b) increased expression of markers for inflammation in each neural region essential for the studied behaviors, and c) loss of regulatory noradrenergic and trophic supports. Tissues from the NaHBED-treated animals exhibited robust normalization of each of these markers. Collectively, our studies demonstrate that: 1) iron deposited via TBI-induced BBB disruption accelerates neuroinflammation and neuronal cell death, and 2) these can be attenuated by an iron chelator treatment. Taken together, iron chelator treatment offers the potential for a mechanism-based therapy that addresses a significant contributor to long-term TBI disabilities, and contributes to trophic support for neuronal and vascular healing, and neuroplasticity for adaptive compensation. NaHBED revealed superior outcomes when compared with treatment using DFO.

Supported by Merit Review Award # 1 I01 RX003123-01A1, from the United States (U.S.) Department of Veterans Affairs Rehabilitation Research and Development Service (RR&D).

Poster 14

Mediation of periventricular white matter hyperintensity burden, cognition, depression, and quality of life in older adults with amnestic Mild Cognitive Impairment

Brittany DeFeis, Jared Tanner, Deirdre O'Shea, Liselotte De Wit, Andrea Mejia, Priscilla Amofa, Sonnie Mayewski, Melanie Chandler, Glenn Smith

Abstract:

Introduction: Periventricular white matter hyperintensities (PVWMH) have been previously associated with the development of depression in older adults, contributing to a vascular theory of late-life depression. Progression of these hyperintensities through development of new clusters or increasing volume has been also associated with cognitive decline and poor depression outcomes, which may impact overall quality of life. Previous studies have suggested that varying numbers and sizes of clusters may indicate specific etiologies and clinical symptoms. The aim of this study is to examine the relationship of the number and sizes of PVWMH clusters on general cognition, depression, and quality of life in older adults with amnestic Mild Cognitive Impairment (aMCI).

Methods: Data for the present study were obtained from 35 older adults with aMCI who completed the baseline assessment as part of a larger ongoing intervention study. PVWMH were extracted using UBO Detector, a cluster-based, automated pipeline which extracts white matter hyperintensities from FLAIR and T1-weighted scans using SPM12 and FSL functions. In this analysis, PVWMH were qualified as total number of clusters (NoC) of various sizes (punctuate [$<10.125mm^3$], focal [$<30.375mm^3$], medium [$<50.625mm^3$], and confluent [$>50.625mm^3$]), and total volume. Mediation analyses were performed predicting whether the impact of PVWMH on quality of life was mediated by cognition and depression when controlling for age, gender, and education.

Results: Participants were, on average, 75.05 (.50), 58% women, and had 16.8 (2.8) years of education. Average cognitive performance on the DRS was 130.49 (8.64), and the average depression score was 10.28 (6.89). Quality of life scores ranged from 33 to 50 (M=40.62; SD=4.66). The number of focal white matter hyperintensity clusters was significantly associated with lower quality of life and higher depressive symptoms. Mediation analyses revealed that the indirect effect of white matter on quality of life as mediated by depression was statistically significant (Effect= -.321; Boot CI= -.684 to -.092). No association between PVWMH and general cognition was detected.

Discussion: Depression fully mediated the relationship between PVWMH and quality of life. There was no relationship found between PVWMH and general cognition, which can be expected given conflicting findings in the literature. The association between the number of PVWMH clusters, rather than total volume, and depression may warrant consideration of etiological differences, and represent more evidence towards the vascular hypothesis for late-life depression.

Poster 15

Age-Related Decreases in CA3-CA1 Ripple Coordination

Nick M. DiCola, A.L. Lacy, O.J. Bishr, K.M. Kimsey, K. Diba, S.N. Burke, A.P. Maurer

Abstract:
Local field potential oscillations are generated by the superposition of synaptic activity. Therefore, changes in hippocampal oscillations are capable of providing insights into the synaptic alterations that occur during aging and neurodegenerative diseases such as Alzheimer's disease. In the hippocampus, high-frequency oscillations known as ripples can be detected in the pyramidal layer and are observed most frequently during rest and 'offline' periods. Ripples are thought to support several cognitive functions including reactivation and memory consolidation; however, most of these studies have focused on the CA1 subregion. Ripples can also be detected in the CA3 pyramidal cell layer and these events, along with their associated sharpwave, are thought to initiate ripple events in CA1 through a large, transient, excitatory drive to the stratum radiatum of CA1. During aging, the hippocampus exhibits several synaptic alterations including CA3 hyperexcitability, loss of Schaffer collateral synaptic efficacy, and hilar interneuron functional loss. Moreover, the frequency of CA1 ripples has been shown to be reduced in aged compared to young rats. Each of these age-associated changes could impact ripple dynamics across the hippocampus, but CA3-CA1 ripple co-occurrence has not been interrogated in the context of age-related cognitive decline. The current study recorded from the right CA1 and CA3 hippocampal subregions of young (4 month) and aged (24 month) rats using two different 64 channel silicon probes. We recorded extracellular local field potentials and examined ripples during rest periods that flanked an epoch of behavior on a hippocampal-dependent task. CA1-CA3 ripple co-occurrence probability was measured as the portion of the time CA1 ripples occurred within a 100 ms time window of CA3 ripples. Preliminary data showed that the probability of CA3-CA1 ripple co-occurrence is decreased in aged animals, suggesting that the aged CA3 has less influence over CA1 than the young CA3. Further studies are required to determine if the aged CA1 receives a greater proportion of influence from cortical input or if the overall activity level is decreased.

Poster 16

Genetic diversity differentially impacts diffusion MRI measures in cortex and hippocampus of wildtype and 5xFAD mice

M. M. Grudny, S. Neuner, M. Pompilus, A. Dunn, M. Febo, C. C. Kaczorowski

Abstract:
Genetic mutations in amyloid precursor protein (APP) and presenilin-1/2, each of which lead to an increase in toxic beta-amyloid, are linked to a high risk of Alzheimer's disease (AD). However, the extent to which individual genetic variation affects neurobiological factors to regulate resilience/vulnerability to cognitive and non-cognitive symptoms of AD is not well understood. To begin to address this gap, the present study investigated brain-wide microstructural characteristics of genetically diverse mice expressing the 5xFAD transgene, each of which show differential susceptibility to AD-related symptoms. Specifically, we used high angular resolution diffusion MRI (HARDI) and quantified well-known diffusion tensor imaging (DTI) metrics such as the fraction anisotropy (FA) and mean diffusivity (MD), along with intracellular volume fraction (neurite density, NDI) and orientation dispersion (ODI) to investigate detailed morphological differences in hippocampal and cortical tissue. Young (6-8 m.o.) and aged (>12 m.o.) male and female 5xFAD mice on C57BL/6 (B6), F1-B6/DBA/2J (D2), or various BXD backgrounds, and their sex- and age-matched wildtype counterparts, were imaged at 11.1 Tesla. Two-way ANOVA indicated a significant strain x mutation effect in the primary motor cortex and dorsal hippocampal commissure of the D2 strain for FA, and in left and right entorhinal cortex and subiculum of BXD strains (Bonferroni $p < 0.05$). These results suggest that strain-specific variation in cognitive outcomes previously demonstrated to exist in this panel (Neuner et al 2019) may perhaps be due to strain-specific variation in 5XFAD-induced microstructural alterations. Background strain was also seen to effect measures including MD, FA, NDI, and ODI in a broad range of brain regions implicated in learning and memory. We are currently processing functional magnetic resonance (fMRI) data sets in order to determine the effect of background strain on brain networks and testing a broad range of behaviorally-phenotyped and genetically-characterized F1-B6/BXD recombinant lines. Results that highlight brain regions involved in resilience to high-risk AD mutations may improve biomarkers for susceptibility and provide clues as to the nature of resilience to AD.

Poster 17

Advanced age and ketogenic diet have dissociable effects across hippocampal subregions

Abbi Hernandez, Caesar Hernandez, Leah Truckenbrod, Keila Campos, Quinten Federico, Jennifer L. Bizon, Sara N. Burke

Abstract:
As the number of individuals living beyond the age of 65 is rapidly increasing, so is the need to develop strategies to combat the age-related cognitive decline that may threaten independent living. Although the link between altered neuronal signaling and age-related cognitive impairments is not completely understood, it is evident that changes in behavioral function are at least partially due to synaptic dysfunction. Aging is accompanied by well-documented changes in both excitatory and inhibitory synaptic signaling across species. Age-related synaptic alterations, however, are not uniform across the brain with different regions showing unique patterns of vulnerability in advanced age. In the hippocampus, increased activity within the CA3 subregion has been observed across species (Wilson, 2005; Yassa et al., 2011), and this can be reversed with anti-epileptic medication (Bakker et al., 2012). In contrast to CA3, the dentate gyrus shows reduced activity with age and declining metabolic activity (Small et al., 2004). Ketogenic diets have been shown to decrease seizure incidence and severity in epilepsy (reviewed in Martin-McGill et al., 2018), improve metabolic function in diabetes type II (reviewed in Feinman et al., 2015), and to improve cognitive function in aged rats. This link between neuronal activity and metabolism suggests that metabolic interventions may be able to ameliorate synaptic signaling deficits accompanying advanced age. We therefore investigated the ability of a dietary regimen capable of inducing nutritional ketosis and improving metabolism to alter synapse-related gene expression across the dentate gyrus, CA3 and CA1 subregions of the hippocampus. Following 12 weeks of a ketogenic (KD) or calorie-matched standard diet (SD), RT-PCR was used to quantify levels of expression of excitatory and inhibitory synaptic signaling genes within CA1, CA3 and dentate gyrus. While there were no age or diet-related changes in CA1 gene expression, expression levels were significantly altered within CA3 by age and within the dentate gyrus by diet for several genes involved in presynaptic glutamate regulation and postsynaptic excitation and plasticity. These data demonstrate subregion specific alterations in synaptic signaling with age and the potential for a ketogenic diet to alter these processes within the brain in dissociable ways across different structures that are uniquely vulnerable in older animals.

Poster 18

LRRK2: LURKING BETWEEN THE BRAIN AND GUT

Mary K Herrick, Madelyn C Houser, Cody E Keating, Lindsey Sniffen, Jianjun Chang, Malú G Tansey

Abstract:

Importance: Links between Parkinson's disease (PD) and the gastrointestinal system have become increasingly common. Mutations in Leucine Rich Repeat Kinase 2 (LRRK2) are known as the greatest genetic contributor to PD and associated with sporadic PD and increased risk for Crohn's disease (CD). G2019S, the most common LRRK2 inherited PD mutation, results in an increased toxic gain-of-function kinase activity. Similarly, the newly identified LRRK2 N2081D SNP results in a gain-of-function increase in kinase activity; and it is associated with a two-fold higher risk for CD, highlighting the need to further understand LRRK2's role in PD and CD.

Objectives: Given the role of LRRK2 in PD and CD, we sought to directly investigate the role of increased LRRK2 protein and increased gain-of-function kinase activity on the gut-brain axis.

Methods: BAC transgenic mice overexpressing mouse wildtype or G2019S LRRK2 were subjected to acute DSS-induced colitis and monitored daily for weight loss and disease activity indexes.

Results: Data suggests G2019S mice are more susceptible to acute DSS-induced colitis. Due to this intestinal insult, G2019S mice exhibited: increased colonic inflammation, altered colonic tight junction proteins, a reduction in CD4 T cell PBMC populations, increased CD8 T cell infiltration to the brain and increased microglia antigen presentation.

Conclusions: G2019S mice are more susceptible to intestinal inflammation thereby resulting in increased neuroinflammation and neuropathology. Given that anti-tumor necrosis factor (TNF) therapy reduces the risk of PD in patients with irritable bowel disease, ongoing studies are determining if soluble TNF (sTNF) inhibition rescues G2019S phenotypes. Completion of these studies will advance our understanding of alterations in LRRK2 levels and activity to the gut-brain axis and may reveal therapeutic opportunities for the use of sTNF inhibitors to delay or mitigate peripheral (gut) inflammation to lower the risk of brain inflammation and age-related neurodegeneration.

Poster 19

The axolotl as a novel model of neurodegenerative disease and neuroresilience

Lucas James, Ariel Walker, Trey Polvadore, Malcolm Maden, Jada Lewis

Abstract:
The axolotl*, Ambystoma mexicanum,* has the ability to regenerate entire limbs, tail, and large portions of organs, making it a widely used model for investigating development and regenerative processes. The axolotl brain exhibits both extensive regeneration and continual production of physiologically healthy and functionally diverse neurons, making it a potentially ideal model for investigating physiological response to neurodegeneration. While the full 32 billion base pair genome was primarily sequenced to identify genes responsible for skin and limb regeneration, we identified homologs for genes associated with neurodegenerative diseases such as *GRN* and *MAPT* to illustrate this model's potential. *GRN* codes for progranulin (PGRN), a 593 AA anti-inflammatory, secreted glycoprotein which can be cleaved into 7.5 cysteine-rich, pro-inflammatory granulins, whereas *MAPT* codes for tau, a 441 AA protein involved in microtubule assembly and stabilization. Using the axolotl-omics genome browser and transcriptome assembly, we identified axolotl genes and transcripts homologous to *GRN* and *MAPT*, coined *ax_grn* and *ax_mapt* which code for ax_pgrn and ax_tau, respectively. We then aligned the protein sequences of PGRN and tau with ax_pgrn and ax_tau using the NCBI Protein BLAST tools and identified corresponding functional domains. The ax_pgrn is 851 AA long and appears to have 10.5 granulin-like motifs that contain the same number of cysteine residues as human granulins. The ax_tau is 528 AA long and has high conservation in the proline-rich, microtubule binding, and C-terminus regions. The ax_tau binding domain is 94% functionally-equivalent to the binding domain of human tau and the proline-rich regions has a similar ratio of prolines. We have repeated this analysis for several other genes implicated in neurodegenerative diseases. Additionally, size is currently used as the aging marker in axolotl research, however, we show that axolotls develop lipofuscin, a wear-and-tear pigment used as a marker in human aging. Establishing the axolotl as a novel model to study neurodegenerative disease potentially enables researchers to study evolved mechanisms of combatting neural damage and pathological protein aggregation.

Poster 20

Neuropathological outcomes in a mouse model of amyloid β and tau

Emily J Koller, Kristen R Ibanez, Elsa Gonzalez De La Cruz, Timothy Machula, Daniel Ryu, Benoit I Giasson, David R. Borchelt, Paramita Chakrabarty

Abstract:
Amyloid β (Aβ) plaques and tau neurofibrillary tangles (NFTs) are the two hallmark pathologies of Alzheimer's disease (AD), but how these two pathological components of AD influence each other is unclear. It has been hypothesized that tau and Aβ synergize to produce the AD pathological cascade which results in neurodegeneration and cognitive impairment, but it remains unknown whether insoluble NFT tau or soluble form(s) of tau synergize with Aβ to produce the pathological effects. To examine the how tau and Aβ interact with each other, we used adeno-associated virus (AAV) to deliver different human tau variants (WT, P301L or S320F) in the TgCRND8 mouse model of Aβ plaques. These tau variants were delivered via intracerebral injection of AAV in neonatal TgCRND8 litters or into the hippocampus of adult 3 month old TgCRND8 mice. Expression of these different tau variants result in either accumulation of abundant soluble hyperphosphorylated tau (WT and P301L) or primarily NFT-type tau (S320F) in nontransgenic mice.

At 3 months of age, AAV-tau expression in neonatally injected TgCRND8 mice led to the accumulation of phosphorylated tau in all the experimental groups, with NFT-type tau and robust widespread astrogliosis observed exclusively in the S320F tau-expressing mice. While expression of WT tau or P301L tau expression did not alter Aβ plaques, expression of AAV-S320F tau increased Aβ plaque burden. We also observed modest levels of tau in the sarkosyl-insoluble cellular fraction of P301L tau expressing TgCRND8 mice (not observed in nontransgenic mice), indicating that the solubility of P301L tau may be altered in the presence of Aβ. In adult TgCRND8 mice, the expression of P301L tau in the hippocampus led to increased levels of MC1 pre-tangle tau, compared to mice injected with AAV-tau at neonatal day P0. These results indicate that presence of Aβ plaques can modify solubility of P301L tau variant. Overall, we conclude that tau variants affect neuroinflammation, Aβ burden, and self-aggregation to differential degrees in the presence of Aβ plaques, leading to the concept that these variants might represent different tau conformers.

Poster 21

Does systemic inflammation contribute to the senescent synapse?

Ashok Kumar, Jolie Barter, Asha Rani, and Thomas C. Foster

Abstract:
Low-grade chronic systemic inflammation during aging is associated with poorer cognitive performance. The current study was design to address the question of whether systemic inflammation contributes to a decrease in hippocampal synaptic transmission and redox mediated decline in NMDA receptor function, which are characteristic of aged-memory impaired animals. Young (5-6 months) Fischer 344 X Brown Norway hybrid rats were injected once a week, for six weeks, with either lipopolysaccharide (LPS) (1 mg/kg, i.p.) or vehicle. Starting 72 hr after the final LPS/vehicle injection, we performed *in vitro* slice electrophysiological recording from CA3-CA1 hippocampal synapses. An input-output curve was generated for total synaptic response across different stimulation intensities for vehicle (n=7/4 slices/animals) and LPS (n=8/4 slices/animals) treated animals. A repeated-measures ANOVA across stimulation intensities indicated an interaction of treatment by stimulation intensity [$F(8,104)=4.029$, $p<0.001$] due to a decrease total synaptic response in slices from LPS animals. Following assessment of total synaptic responses, the NMDA receptor mediated synaptic component was pharmacologically isolated, and input-output curves were generated from vehicle (n=7/4 slices/animals) or LPS (n=7/4 slices/animals) treated animals. A repeated-measures ANOVA across stimulation intensities indicated an interaction of treatment by stimulation intensity [$F(8,96)=3.3$, $p<0.01$], due to a decrease in the NMDA receptor response for LPS-treated animals. The role of redox stress in the decline of the NMDA receptor mediated synaptic component was also tested. After collection of baseline responses, the reducing agent, dithiothreitol (DTT) was added to the bath and responses were measured for 60 minutes. No group differences were observed following addition of DTT, which increased the NMDA receptor synaptic response by 127±10% (3/6 animals/slices) in the vehicle control group and 123±3% (4/7 animals/slices) in the LPS group, indicating no redox effects at this time point. We suggest that synapse elimination underlies LPS-mediated decrease the total and NMDA receptor synaptic transmission. However, transcriptional evidence indicates that younger animals exhibit considerable recovery at the 72 hr time point. Preliminary results suggest that a redox mediated NMDA receptor hypofunction may be present within 24 hr after LPS treatment.

Poster 22

Aberrant response based strategies in old age are related to elevated *Arc* expression in the Dorsal Striatum

Katelyn N. Lubke, Sean M. Turner, Luis M. Colon-Perez, Marcelo Febo, Sara N. Burke

Abstract:
In advanced age, rats are slower to acquire the object-in-place rule on a bi-conditional association task (Hernandez et al., 2015) and to learn to discriminate between objects that share features (Johnson et al., 2017). On these tasks, poor performance is associated with response-driven behavior in which an animal is biased to select an object on a particular side (left versus right) regardless of the feature information of test stimuli. While it has been reported that this response-driven behavior is facilitated by the dorsal striatum (Packard and McGaugh, 1992; Gold, 2004), the neurobiological mechanisms underpinning these cognitive impairments are not completely understood. We recently showed that response-driven behavior correlated with elevated resting state functional connectivity between the anterior cingulate cortex and dorsal striatum (Colon-Perez et al., 2018), but it is unknown if this relates to neural activity during task performance. The current study tested rats on the working memory/bi-conditional association task (WM/BAT), which measures an animal's ability to select an object in a pair-wise discrimination problem based on the location on the maze while simultaneously performing a continuous alternation task. Five young (4 months old) and 4 aged (24 months) Fischer 344 x Brown Norway F1 hybrid rats were trained for 14 days on the WM/BAT. While young rats learned the object-in-place rule within that time frame, the aged rats failed to reach criterion performance and showed a significantly higher response bias compared to the young animals. On the final day of testing, rats completed the WM/BAT and a control alternation task and then sacrificed by rapid decapitation to label brain tissue for expression of the activity-dependent immediate-early gene *Arc* (Guzowski et al., 2001). When *Arc* expression in the dorsal striatum and anterior cingulate cortex was analyzed to identify neurons active during the WM/BAT and alternation task, it was observed that the proportion of active cells within the anterior cingulate cortex during both tasks was similar between young and aged rats. In contrast, in the dorsal striatum more cells were active during WM/BAT in aged compared to young rats. This pattern of elevated *Arc* expression was not observed during the alternation task. Together these data suggest that elevated activity in the dorsal striatum is associated with an increase in the use of a suboptimal response-based strategy in aged rats, which could contribute to enhanced functional connectivity between the striatum and other cortical regions.

Acknowledgments: This work was supported by National Institutes of Health National Institute on Aging grants R01 AG049722 and P50 AG047266, and the McKnight Brain Research Foundation.

Poster 23

ROLE OF PGE_2 EP1 RECEPTOR ANTAGONIST ON STROKE OUTCOMES IN ALZHEIMER DISEASE MOUSE MODELS

Fulvio R Mendes, Jenna L Leclerc, Lei Liu, Pradip Kamat, Damian Hernandez, Arash Naziripour, Abdullah S Ahmad, Sylvain Dore

Abstract:

Background: AD is the most common memory disorder and its prevalence is expected to triple by the year 2050. Neuroinflammation is recognized as an important player in the pathogenesis of AD. One of the most recognized pathways in mediating the neuroinflammation is of prostaglandin E_2 (PGE_2) EP1 receptor pathway. Role of PGE_2 EP1 receptor in AD mouse models following stroke has not been studied. In this study, we examined the efficacy of a selective EP1 antagonist, ONO-8713, on lesion volumes and behavioral indexes in AD mouse models after stroke. Methods: Two cohorts of transgenic, APP/PS1 and 3xTg, and wildtype (WT) mice were subjected to permanent distal middle cerebral artery occlusion (pdMCAO) and sham surgeries. EP1 antagonist ONO-8713 or vehicle was then administered to analyze its effect on anatomical and functional outcomes. Results: The functional outcomes were significantly deteriorated in the APP/PS1 and the 3xTg mice after stroke. Interestingly, the ONO-8713-treated groups of WT mice performed significantly ($p<0.001$) better in open field test than the respective groups of 3xTg mice. For the passive avoidance test, APP/PS1+ONO-8713 mice exhibited significant ($p<0.05$) difference in retention as compared with the vehicle group; whereas, there was a significant difference in acquisition between WT+ONO-8713 and 3xTg+ONO-8713 ($p<0.05$). There was a significantly lower tissue injury in APP/PS1+Veh mice when compared to the APP/PS1+ONO-8713 mice ($p<0.02$). Percent tissue injury was significantly higher in APP/PS1+ONO-8713 mice when compared to WT+ONO-8713 mice ($p<0.05$). Similarly, in the 3xTg cohort, percent tissue injury and percent tissue loss were significantly higher in 3xTg+ONO-8713 mice than in WT+ONO-8713 mice ($p<0.02$). Conclusion: The EP1 receptor antagonist ONO-8713 shows some beneficial effects on functional and anatomical outcomes after stroke in APP/PS1 and 3xTg mice models of AD; though, the effects were not significant in all outcomes investigated. Further studies are needed to understand the role and optimal timing of EP1 receptor blockade in the context of AD etiopathology. Funding support: Grants from the São Paulo Research Foundation, FAPESP (FRM), NIH, and the Ed and Ethel Moore Alzheimer's Disease Research Program (SD).

POSTER 24

Longitudinal characterization of sex differences in functional and cognitive decline during aging

Asha Rani, B. Yegla, J. Barter, A. Kumar, M. Febo, K. Esser, and T. C. Foster

Abstract:
Variability in cognitive decline during aging is related to biological factors (e.g. sex) and the history of experience (e.g. environmental enrichment, previous testing) and lifestyle factors (diet, exercise). In order to understand the contribution of these factors and underlying mechanisms, longitudinal studies are required to define when cognitive decline first emerges. An important caveat for longitudinal studies is the need to control for practice and carry-over effects, associated with multiple testing, which could mask the effects of aging. The current longitudinal study was designed to examine the role of biological and behavioral factors that might predict the variability in age-related cognitive decline. Fischer-344 male (n = 10) and female (n = 10) rats were first characterized at 6 months. Behavioral tests included physical ability (grip strength, Rotarod, and activity wheel), anxiety (neophobia and open field activity), episodic memory (water maze delayed match to place and novel object recognition), and a circadian stress test of resiliency. These measurements were repeated at 12 and 18 months. Sex differences were observed as increased grip strength for males (6 mon: $p < 0.01$, 12 mon: $p < 0.005$, 18 mon: $p < 0.005$). Females exhibited increased activity (6 mon: $p < 0.001$, 12 mon: $p < 0.0001$, 18 mon: $p < 0.0001$). Females also exhibited better Rotarod performance ($p < 0.01$) at 12 mon. In general, neophobia and open field activity declined across testing sessions in the absence of a consistent sex difference. A decline in episodic memory for longer delays (30 and 120 min) emerged at 12 month, particularly for males. Within sex comparisons confirmed that males exhibited a decline in episodic memory during aging. Functional magnetic resonance imaging measures indicated impaired memory was associated with changes in functional connectivity, which suggest compensatory mechanisms. Currently, analysis is focused on the circadian stress test of resiliency and other biological measures. The results of the current study demonstrate sexual dimorphism in the onset and trajectory of cognitive decline.

Funding:
NIH Grant R01AG037984
NIH Grant R37AG036800
NIH Grant R01AG052258
NIH Grant R01AG049711
Evelyn F. McKnight Brain Research Foundation

POSTER 25

Effect of age and estrogen on whole genome DNA methylome profiling of CpGs in CA1 region of the hippocampus.

Puja Sinha, Ashok Kumar, Asha Rani, and Thomas C. Foster

Abstract:
The ability of estradiol (E2) to improve hippocampal-dependent memory declines with advanced age and prolonged E2 deprivation, indicating a closing of the E2 therapeutic window. Similarly, the ability of E2 to induce transcription of synaptic plasticity genes in the hippocampus deteriorates with advanced age. We hypothesize that during aging, epigenetic modification through DNA methylation renders these genes unresponsive to E2. Estrus cycle was checked by vaginal lavage before and after ovariectomy (OVX) to confirm the loss of E2. Young and middle aged (MA) rats were cycling at regular intervals while two out of six aged animals had an irregular estrus cycle prior to OVX. Six weeks following OVX, two injections of E2 (10 µg: young, n = 4; MA, n = 3; aged, n = 4) or oil (young, n = 2; MA, n =2; aged, n = 2) were given 24 hours apart. The hippocampal CA1 region was collected 6 hours following the second E2/Oil injection and flash frozen. Genomic DNA was isolated. Following sodium bisulfite conversion of genomic DNA, whole genome bisulfite sequencing (WGBS) was performed. WGBS libraries were constructed with the Illumina Truseq DNA Methylation kit, and libraries were paired-end sequenced with the Illumina HiSeq3000 (2X150 cycles). Data analysis was performed using the differential methylation analysis pipeline to detect differentially methylated regions (DMRs) as well as the differential CpG methylation in promoters and gene bodies. The majority of identified CpG sites (> 90%) were found in gene body regions. Methylation analysis of E2-treated relative to age matched oil-controls indicated decreasing effect of E2 on differential CpG methylation with advancing age, particularly for hypomethylation following E2 treatment: young (hyper/hypo-653/660 sites), MA (hyper/hypo-555/485 sites), and aged (hyper/hypo-553/291 sites). Similarly, DMRs for E2 treatment were 113, 59 and 45 in young, MA, and aged treated groups, respectively. The results support a decrease in E2 induced differential methylation with advanced age. Gene ontology (GO) was used to examine gene clustering for hypermethylated and hypomentylated genes in E2 treated versus controls within each age group. A treatment associated enrichment was observed for MA hypomethylated genes (cAMP signaling pathway) and hypermethylated genes for aged animals (calcium-dependent membrane targeting). Comparisons between control groups indicated hypermethylation of synaptic signaling genes in MA relative to young control. The results are consistent with hypermentylation contributing to an age-related **1)** decreased expression of synaptic genes and **2)** decreased E2-responsive transcription.

Funding:
NIH Grant R01AG037984
NIH Grant R37AG036800
NIH Grant R01AG052258
NIH Grant R01AG049711
Evelyn F. McKnight Brain Research Foundation

POSTER 26

Impaired Pattern Separation During Aging is Associated with Altered Hippocampal Gene Transcription

Garrett Smith, Asha Rani, Ashok Kumar, and Thomas Foster

Abstract:
Previous studies of age-related transcriptional changes indicate that cognitive impairments are associated with differentially expressed genes (DEGs) linked to defined neural systems (e.g. episodic memory-CA1, executive function-prefrontal cortex). These findings provide information on possible molecular mechanisms for age-related cognitive decline. Aging is also associated with a deficit in pattern separation (PS), the generation of distinct mnemonic representations from overlapping experiences. The dentate gyrus (DG) is implicated in PS and exhibits several age-related changes (e.g. decrease in neurogenesis, impaired synaptic plasticity, and loss of afferent input) that could impair PS performance. We hypothesize that aged animals with impaired PS ability will express a distinct transcriptional profile relative to unimpaired animals, specifically within the DG and not in other hippocampal subregions. We used a modified water maze beacon discrimination task to characterize PS in young (5 mo, n=12) and middle-age (12 mo, n=16) F344 male rats. This was followed by a reference memory task. Middle-age rats showed deficits in discriminating two identical beacons compared to young, when trials began with the rat positioned equidistant between the two beacons (p=0.005). Reference memory performance between these two age groups was not significantly different (p=0.2); however, older animals appeared to compensate for impaired for PS though greater reliance on reference memory. Following behavioral testing, mRNA sequencing was performed on hippocampal subregions DG, CA1, and CA3. The DG exhibited more age-related DEGs compared to CA1 and CA3. Likewise, middle-age rats impaired on the PS task showed more DEGs in the DG than in CA1 or CA3, compared to age-matched unimpaired rats. Functional annotation clustering of impaired animals highlighted dysregulation of genes related to RNA processing and protein folding in the DG, downregulation of inflammation-related genes in CA1, and no significant cognition-related gene dysregulation in CA3. These results suggest: 1) the beacon task is sensitive to age-related PS impairment, 2) the three hippocampal regions age independently, and 3) regional differences are reflected in differential use of strategies to solve the task.

POSTER 27

Exacerbation of tauopathy in a mouse model of Alzheimer's disease

B. Ulm, G. Xu, S. Fromholt, J. Howard, D. Borchelt, J. Lewis

Abstract:

Rationale and Objective: Alzheimer's disease (AD) is diagnosed based on the presence of amyloid plaques and neurofibrillary tangles composed of tau. While tau aggregates are primary pathologies in many other neurodegenerative diseases, the presence of extracellular amyloid beta (Aβ) deposits sets AD apart. Studies of familial AD patients has largely demonstrated that amyloid pathology precedes tau pathology, but replicating this temporal relationship of familial AD in mouse models has been challenging.

Methods: In the present study, we generated a mouse model with both hallmark pathologies of AD, by crossing the APPswe-PS1dE9 model of Aβ amyloidosis with mice that express 0N4R P301L human tau under transcriptional regulation of a doxycycline-suppressible system (rTg4510 mice). From conception onward, doxycycline was administered to suppress transgenic tau expression, while allowing Aβ pathology to progress (14-15 months). Thereafter, doxycycline administration was halted, allowing for induction of human P301L tau expression for the following 6 months of age.

Results: The APPswe-PS1dE9/rTg4510 mice (14-15 months transgenic tau suppression, 6 months transgenic tau expression, n=8) exhibited an exacerbated tau pathology compared to rTg4510 mice expressing only mutant tau with the same treatment (n=9). The exacerbation of tau pathology in this model recapitulates the chronological progression of pathology proposed in the amyloid cascade hypothesis and demonstrates the priming effects of early amyloid pathology on late-life tau pathology. Studies to assess both inflammatory and neurodegenerative changes are ongoing.

POSTER 28

Progranulin deficiency causes early structural abnormalities in the periphery of knockout mice

Ariel Walker, Sruti Rayaprolu, Jennifer Gass , John Howard, Lucas James, Colin Duffy, Jada Lewis

Abstract:
Progranulin (PGRN) is a secreted glycoprotein that can be cleaved into granulin motifs depending on the biological needs of the body, with full-length PGRN acting as an anti-inflammatory molecule. Mutations within the granulin gene (*GRN*) exert pleiotropic effects as heterozygous loss-of-function mutations cause frontotemporal lobar dementia with TDP-43 pathology (FTLD-TDP43) and homozygous loss-of-function mutations cause a rare form of neuronal ceroid lipofuscinosis (NCL). Mice deficient of *Grn*, develop excessive intraneuronal accumulations of lipofuscin throughout the brain, a pathological hallmark of NCL. Current studies of NCL pathology have been mainly focused in the brain, but PGRN is also expressed throughout the periphery; therefore, we sought to determine whether *Grn*-deficient mice develop NCL relevant pathology in organs peripheral to the brain. We assessed the liver, kidney, lung, and heart from 7 and 12-month-old *Grn*-knockout (KO) (N=4) and wild-type (WT) (N=4) mice per age using immunohistochemical stains and immunoblotting. The livers of the KO mice show abnormal hepatocyte structure, glycogen deposits, and enlarged lysosomes and macrophages at 7 and 12 months compared to the WTs. Cathepsin Z and TFEB are both elevated in 7-month-old KO kidneys compared to 7-month-old WT kidneys. Lastly, the lungs and hearts of the KO mice do not have any overt differences in pathology compared to the WTs at 7 and 12-months of age. These data highlight the presence of peripheral pathologies due to PGRN loss and raise the potential that peripheral symptoms may be overlooked in patients with PGRN deficiency. Although obtaining brain tissue is rare from individuals carrying homozygous *GRN* mutations, peripheral tissue biopsies, such as liver or kidney, can be taken in relatively non-invasive procedures and peripheral pathology could then serve as a peripheral marker for disease progression and treatment.

POSTER 29

Sex Differences in Exercise-induced Extracellular Vesicle Release and Cognitive Enhancement

Yegla, Brittany, Esser, K., Foster, T.C.

Abstract:

Aging is characterized by a substantial loss of muscle mass and strength, which is associated with higher mortality. Exercise can not only mitigate age-related frailty and muscle weakness but also improve metabolic, cardiovascular, and cognitive function. The mechanism by which exercise exerts these effects remains to be elucidated. Thus, this study examines age- and sex-related differences in exercise-induced intercellular signaling, specifically extracellular vesicles (EV) and their miRNA content, and how this relates to changes in muscle, cognition, inflammation, and redox state in multiple organs with exercise. One cohort of young and aged (6 & 24 mo) male and female Fischer-344 rats (N=4/group) underwent treadmill running for a single bout of exercise at 70% VO_{2max} to determine maximal plasma EV release post-exercise (<15, 90, 180min after). A second cohort ran on treadmills for two months on a progressive workload schedule to elicit 70% VO_{2max}. Following exercise rats were evaluated for physical and cognitive changes compared to sedentary controls. After a final bout of exercise, rats were euthanized, and blood, muscle, liver, kidney, brain, and fat were collected to examine the impact of age, sex, and exercise on EV-derived miRNA expression, redox levels, and inflammatory markers. For the first cohort, CD-63+ EVs displayed a relative increase 90min after acute treadmill running (z-score; control: -0.24±0.22; <15min: 0.04±0.28; 90min: 0.30±0.29; 180min: -0.10±0.20). This timepoint was utilized for euthanizing the second cohort. Interestingly, young females released significantly more EVs after exercise than young and aged males (p<0.02) and aged females released more than young males (p=0.01). For behavioral measures, repeated exercise elicited sex-specific effects in open field measures ($F_{1,20}$=5.21, p=0.03), where female runners moved more than other rats (p<0.05). They also froze less during contextual fear conditioning (p<0.05) and throughout cued extinction (p<0.01) compared to controls. Exercise enhanced cognitive performance on a hippocampal task (context-object discrimination; $F_{1,19}$=4.69, p=0.04), with all runners exploring a context-incongruent object more than controls. Next-generation sequencing of EV miRNA and inflammatory quantification are currently being conducted. It is predicted that continued exercise will shift the aging secretome to resemble a younger profile. Overall, these data are the first to demonstrate a sex-specific effect of exercise on EV release and physical and cognitive measures, which may allude to differential exercise-induced EV content in males and females.

POSTER 30

Translational rat model of cognitive aging using a touchscreen operant platform to test visual discrimination and association

Sabrina Zequeira, Sarah A. Johnson, Meena Ravi, Samm Smith, Andreina Hampton, Leslie S. Gaynor, Andrew P. Maurer, Jennifer L. Bizon, Sara N. Burke

Abstract:

Animal models play an essential role in the development and testing of therapeutic treatments for cognitive dysfunctions that occur in advanced age and neurodegenerative diseases. While behavioral paradigms for testing animal models are carefully designed to enable an understanding of neurobiological mechanisms of cognitive impairments, tasks administered to rodents often do not closely resemble those used with human study participants. In fact, in clinical and research settings humans are often tested with computer monitors that display images of visual stimuli. In contrast, rodent cognition is frequently assessed in large mazes using 3-dimensional objects as test stimuli. One test frequently administered to humans is The Cambridge Neuropsychological Test Automated Battery (CANTAB) which is a series of neuropsychological assessments that can be used to assess age-related cognitive changes. These tests include the Paired Associates Learning (PAL) task which is a visuospatial learning task (Talpos et al 2008) that can readily be adapted for screening rodent cognition. During the PAL task, in rodents, three visual patterns (A, B, and C) are associated with three touchscreen locations; 1,2, and 3 respectively. On a given trial, the rodent must choose between a stimulus presented in its correct location (e.g. A1) and a stimulus presented in one of its two incorrect locations (e.g. B3). Humans with Alzheimer's disease (AD; Égerházi et al. 2007) and rodent models with damage to brain regions vulnerable in AD (Talpos et al., 2009) are impaired on this task, but it has not yet been used to screen for cognitive decline associated with normal aging in rodents. Another test used to assess cognitive function in older adults is the Mnemonic Similarity Task (MST) (Kirwan & Stark 2007; Yassa et al., 2010; Stark et al., 2013), which measures participants ability to discriminate between stimuli that share overlapping features. During the rodent variant of the MST, two images are displayed on a computer monitor. One is the rewarded target object and the other image is a lure object of varying feature overlap with the reward object. On a given trial, the rodent must choose between the rewarded target image and the incorrect lure. The current study assessed performance of adult (10-12 months), and aged (26-30 months) Fischer 344 x Brown Norway F1 hybrid rats on the PAL task and the newly developed rodent variant of the MST in a touchscreen platform. Performance across tasks was assessed to identify potential differences in performance in both discrimination and associative memory in aged animals. Future research utilizing cross-species behavioral paradigms can work to advance our understanding of the underlying neurobiological mechanisms of cognitive decline in advanced age and neurodegenerative diseases such as AD.

Ronald Lazar, Ph.D.
Director
Evelyn F. McKnight Chair for Learning and Memory in Aging

Erik Roberson, M.D., Ph.D.
Associate Director

POSTER 31

Effects of X-irradiation on Neuronal and Circuit Function

Aundrea F. Bartley, Micah E. Bagley, Justin A. Barnes, David N. French, Timothy R. Totsch, Gary M. Gray, Lori L. McMahon, and Lynn E. Dobrunz

Abstract:
Optogenetics is a widely used technique in neuroscience. However for in vivo studies, the invasive nature of current methods for light delivery into the brain can cause damage to brain regions of interest, potentially confounding the results. Therefore, it is desirable to develop less invasive methods of light generation in the brain for in vivo optogenetics. One potential method to stimulate in vivo optogenetics would use X-ray activation of radioluminescent materials. X-rays are ideally suited for use in optogenetics because the beam can maintain focus through the tissue with little scattering. However, high levels of X-irradiation have been shown to cause cognitive dysfunction and neuronal death. Little is known about how lower levels of X-irradiation affects synaptic transmission. In this study, extracellular and whole cell electrophysiology methods are used to investigate the acute effects of X-rays on neuronal health and overall circuit function at various doses, up to 5 Gy. In preliminary experiments from cell culture, low levels of X-ray exposure alone did not depolarize neurons or stimulate synaptic transmission. Furthermore, in acute hippocampal slices, low levels of X-rays had no effect on basal synaptic transmission. However, the highest dose used did cause a modest reduction of basal synaptic transmission. Next, we tested for effects of X-irradiation on long-term potentiation, a more robust measurement of synaptic health and integrity. Long-term potentiation could still be induced at all levels of X-ray tested. Together, these results indicate that neuronal function and synaptic plasticity are intact during low levels of X-ray exposure. Because X-rays have been shown to cause low level activation of rhodopsin in the retina, we will verify that a low level of X-ray exposure does not itself cause activation of an opsin such as channelrhodopsin-2. In addition, we will test the ability of visible light emitted from radioluminescent materials to activate the opsin. Therefore, these experiments will provide proof of principle that the use of X-ray to activate radioluminescent materials would potentially be a viable tool for noninvasive delivery of light for in vivo optogenetics.

POSTER 32

mTOR complex specific abnormalities in Schizophrenia brain

Radhika Chadha and James H. Meador Woodruff

Abstract:
Cognitive deficits are observed in a majority of schizophrenia (SZ) patients. The AKT-mTOR pathway is an important signaling cascade associated with cognitive dysfunction. This pathway is tightly regulated by differential phosphorylation of key proteins. AKT is a serine-threonine kinase which regulates cell survival, proliferation and growth and requires phosphorylation at S473 and T308 for complete activation. Prior literature suggests reduced expression of AKT in SZ. mTOR is a kinase that forms 2 distinct complexes- mTORC1 and mTORC2. mTORC1 consists of mTOR, Raptor, GβL, PRAS40 and Deptor proteins. It facilitates ribosome biogenesis and protein translation and acts downstream of AKT. mTORC2 consists of mTOR, Rictor, GβL, Protor, mSin1 and Deptor proteins. It plays an important role in actin dynamics and acts upstream of AKT. mTOR is phosphorylated at S2448 and S2481 sites for activation in both complexes. Abnormalities in the mTOR complexes can contribute to dysregulated protein synthesis and actin dynamics, both of which which have been implicated in SZ. Previously, we found decreased levels of AKT and GβL protein expression in SZ brain. Phosphorylated forms of AKT (S473), mTOR (S2448) and S6RP (S235/236 and 240/244) were also found to be reduced. Therefore, in this study, we investigated if there are mTOR complex specific deficits in SZ. We used postmortem dorsolateral prefrontal cortex (DLPFC) from 22 matched pairs of SZ and comparison subjects. The DLPFC plays an important role in cognitive functioning and has widespread evidence in support of its role in SZ. We co-immunoprecipitated mTORC1 using Raptor and mTORC2 using Rictor proteins to determine the structural and functional integrity of each complex. Using western blot analysis, we measured protein expression of raptor, rictor and mTOR, as well as phosphorylation of mTOR in both complexes. To assess the relative abundance of mTOR complexes, we co-immunoprecipitated mTOR and measured the ratio of raptor to rictor. Our findings suggest that the AKT-mTOR signaling pathway is downregulated in SZ DLPFC. Given the importance of this pathway in synaptic plasticity via its regulation of protein synthesis and cytoskeletal organization, these abnormalities may represent a mechanism underlying cognitive dysfunction in SZ.

POSTER 33

Increased glutamatergic transmission at the corticostriatal synapse of PINK1 KO rats

Rose B. Creed, Charlene Farmer, Rosalinda Roberts, Lori L. McMahon, Matthew S. Goldberg

Abstract:
Mutations in the PTEN induced kinase 1 (PINK1) gene cause autosomal recessive Parkinson's disease (PD). The main pathological hallmarks of PD are loss of dopamine neurons in the substantia nigra pars compacta and the formation of α-synuclein rich aggregates termed Lewy body inclusions. We and others have demonstrated that PINK1 knockout (KO) rats have mitochondrial dysfunction, locomotor deficits, and α-synuclein aggregates in different brain regions including the substantia nigra, striatum, and cortex. PINK1 is a mitochondrial targeted kinase involved in the clearance of damaged mitochondria. In neurons, mitochondria are prominently located in the pre-synaptic terminal, where they provide energy needed for vesicle movement and synaptic transmission. Additionally, α-synuclein is also important in synaptic vesicle movement and synaptic transmission. Given the importance of mitochondria to synaptic transmission, and the effect of PINK1 deficiency on mitochondrial health and α-synuclein aggregation, we sought to determine whether PINK1 KO rats have altered synaptic transmission. We hypothesize that PINK1 KO rats have changes in cortical excitatory neurotransmitter release onto spiny projection neurons (SPNs) of the dorsal striatum. Using whole cell patch clamp electrophysiology recordings from SPNs in acute striatal slices of WT and PINK1 KO rats at ages 2, 4, and 6 months, we observed an age-dependent increase in frequency spontaneous glutamatergic EPSCs onto SPNs. In addition, glutamatergic synapses on SPNs in PINK1 KO rats took longer to recover following depletion of the readily-releasable pool of synaptic vesicles with a 50 Hz train. These studies reveal that PINK1 is required for normal corticostriatal synaptic transmission. Ongoing studies will measure the extent to which the altered presynaptic release could be due to impairments in dopaminergic neurotransmission or due to impairments in presynaptic mitochondrial buffering capacity. Furthermore, we will measure whether the impairments in synaptic recovery following depletion may be due to perturbations in synaptic vesicle distribution or alpha synuclein homeostasis.

POSTER 34

Violence exposure contributes to sex differences in the neural response to stress

Elizabeth S. Davis, Adam M. Goodman, Marc N. Elliott, Mark A. Schuster, Susan Tortolero Emory, Sylvie Mrug, David C. Knight

Abstract:
The neural response to stress differs between men and women within multiple brain regions (e.g. prefrontal cortex, amygdala, and hippocampus) that play an important role in emotion expression and regulation (Seo et al., 2013; Seo et al., 2017). However, prior research has not focused on whether violence exposure contributes to sex differences in stress-elicited neural activity. Therefore, the present study investigated the relationship between sex, prospectively assessed violence exposure (ages 11, 13, 16, and 19), and the neural response to psychosocial stress as young adults (mean age = 20.03 ± 1.51). In the present study, 301 participants (149 Men, 152 Women) completed the Montreal Imaging Stress Task (MIST), a psychosocial stress task designed for the neuroimaging environment. Results demonstrated significant sex differences in violence exposure, such that men had greater violence exposure than women [$t(299)=3.35$, $p<0.01$]. Further, a linear mixed effects model revealed significant sex differences in the neural response to stress within the dorsolateral prefrontal cortex (dlPFC) and dorsomedial prefrontal cortex (dmPFC). Specifically, men had greater neural reactivity within the dlPFC and dmPFC than women. In addition, we assessed the interaction between violence exposure and sex on the neural response to stress. Results demonstrated a significant interaction between sex and violence exposure within the right parahippocampal gyrus. The present study demonstrates the relationship between violence exposure and the neural response to stress.

POSTER 35

Primary visual cortex representing central, near peripheral, and peripheral vision are differentially functionally connected, and these differences follow patterns of known brain networks

Pinar Demirayak, Sara Sims, Utkarsh Pandey, Kristina M. Visscher

Abstract:
In primary visual cortex (V1) central and peripheral vision are specialized for different functions. Due to this specialization, interactions between central, near peripheral and far peripheral regions of V1 and other cortical areas are expected to be different. Previous work from our lab found differential functional connection profiles for different eccentricities of vision, and these patterns followed patterns of known brain networks (Griffis et al., 2017). This earlier work had showed strongly significant effects in only 20 participants, and participants were fixating during minute-long breaks between tasks. We sought to replicate this previous work in a larger sample, and also extend the findings to free viewing during rest.

Our resting state analyses were done on3T preprocessed MRI data from the Human Connectome Project (HCP) database. Data used for the primary analyses were acquired from 782 healthy right-handed participants (22-36; M/F=335/447). Additional preprocessing analyses were performed on the residual BOLD data to reduce spurious variance not associated with neural activity. Regions of interests (ROIs) on central, near and far periphery of V1 were defined for seed-to-voxel analyses based on Freesurfer's retinotopy template developed by Benson et al. (2014) within Freesurfer 6.0 segmented gray matter boundaries. Cingulo-opercular, fronto-parietal and default mode networks were identified as seed ROI for seed-to-seed analyses based on Yeo et al. (2011) reference RS networks. For both seed-to-voxel and seed-to-seed analyses, time series from each seed ROI was extracted and its correlations with either all voxels or other seed ROIs were calculated in Matlab.

Our results showed that central, near peripheral and far peripheral sectors of primary visual cortex have different connectivity patterns with non-visual areas. Components of the fronto-parietal control network are tightly functionally connected with central and near peripheral sectors of V1, components of cingulo-opercular control network are tightly connected with near peripheral sectors of V1, components of default mode network are tightly connected with central and far sectors of V1.

These results replicated and extended to a broader context, our previous data (Griffis et al., 2017) by suggesting that visual input that is processed by different sectors of primary visual cortex are prioritized by different large-scale resting state networks. Overall, our findings contribute to the understanding of functional processing of visual information in the healthy young brain and they might serve as a template to compare with abnormal brain functioning.

POSTER 36

Dynamic gene expression in the nucleus accumbens following acute cocaine experience

Corey G. Duke, Jennifer J. Tusche, Robert A. Phillips, Morgan E. Zipperly, Katherine E. Savell, Laura Ianov, and Jeremy J. Day

Abstract:
Drug addiction is a worldwide health problem, with overdose rates of both psychostimulants and opioids currently on the rise in many developed countries. Drugs of abuse elevate dopamine levels in the nucleus accumbens (NAc) and alter transcriptional programs believed to promote long-lasting synaptic and behavioral adaptations. However, even with well-studied drugs such as cocaine, drug-induced transcriptional responses remain poorly understood due to the cellular heterogeneity of the NAc and complex drug actions via multiple neurotransmitter systems. Here, we profiled and analyzed 15,676 cells from the NAc of naïve male and female rats collected 60 minutes after exposure to cocaine (20mg/kg) or saline, creating a comprehensive molecular atlas of NAc cell subtypes. Using this transcriptional map, we characterized cell- and sex-specific responses to acute cocaine experience. We also defined an immediate early gene expression program immediately following dopamine (DA) receptor activation *in vitro*, which marks the transcriptional response of specific neuronal populations to cocaine *in vivo*. Together, these data define the genome-wide transcriptional response to cocaine with unprecedented cellular precision, identify gene expression states which may predict cocaine response, and isolate the transcriptional signature of dopamine receptor stimulation within individual neuronal subpopulations.

POSTER 37

Validation of a new computational approach for presurgical language lateralization in patients with refractory epilepsy

Hyun Freeman, Jeff Killen, Roy C. Martin, Ismail S. Mohamed

Abstract:
Epilepsy affects approximately 1% of the population and is medication resistant in approximately one-third of patients with epilepsy (Schoenberg, Werz, & Drane, 2016). For patients with refractory epilepsy (medication resistant epilepsy), surgery offers a chance of becoming seizure free (Schoenberg et al., 2016). An important presurgical procedure is determining language lateralization in order to avoid language and memory deficits after surgery. Currently the "gold standard" of presurgical language lateralization is the Wada test, however, it is an invasive procedure. A non-invasive method of determining language lateralization is by using magnetoencephalography (MEG) with a word recognition task and processing the data using an equivalent current dipole (ECD) model. However, the method has not been successfully replicated across centers and is also dependent on a high level of patient cooperation. The purpose of this study is to examine if a new computational approach, maximum entropy of the mean (MEM), can be used to lateralize language in patients with intractable epilepsy. MEG data was collected on 15 patients with epilepsy and each patient completed an auditory word recognition task (Papanicolaou et al., 2004). The MEG data was processed using the Brainstorm toolbox and lateralization index (LI) was calculated based on activation scores in areas typically activated during speech processing; the superior temporal gyrus, the middle temporal gyrus, the supramarginal gyrus, pars triangularis, and the transverse temporal gyrus within the first 200 millisecond of each trial. Language lateralization was compared to results from ECD modeling, fMRI, and if available, results from the Wada test. MEM lateralization was concordant with ECD modeling in eight patients. MEM lateralization was superior to ECD in three patients confirmed by results from either the Wada or fMRI. MEM lateralization was discordant with fMRI and ECD in one patient. Based on the preliminary data, the Brainstorm toolbox, MEM is a promising tool that could be used to determine language lateralization in patients with epilepsy and lateralized response to words can be elicited within the first 200 millisecond of an auditory word task.

POSTER 38

Defining α-synuclein species responsible for Parkinson's disease phenotypes in mice

J. M. Froula, M. Castellana-Cruz, N. M. Anabtawi, J. Camino, S. Chen, D. R. THRASHER, J. Freire, A. A. Yazdi, S. Fleming, C. Dobson, J. Kumita, N. Cremades, L. Volpicelli-Daley

Abstract:
Parkinson Disease (PD) is a neurodegenerative disorder characterized by fibrillar neuronal inclusions composed of α-synuclein. α-Synuclein exists in multiple structural forms including disordered, non-amyloid oligomers, ordered amyloid oligomers, and fibrils. It is critical to understand which conformers contribute to specific PD phenotypes. In this study, we utilized a mouse model to explore the effects of stable amyloid β-sheet oligomers compared to fibrillar α-synuclein. These species were characterized biophysically using transmission electron microscopy, atomic force microscopy, circular dichroism spectroscopy, Fourier transform-infrared spectroscopy, and thioflavin T assays. The different forms of α-synuclein were then unilaterally injected into the striatum to determine their ability to induce PD-related phenotypes. We show that β-sheet oligomers produce a small but significant loss of dopamine neurons in the substantia nigra pars compacta (SNc). Injection of small β-sheet fibril fragments, however, produces the most robust phenotypes; significantly reduction of striatal dopamine terminals, SNc loss of dopamine neurons, and appearance of motor behavior defects were detected. Thus, although the β-sheet oligomers cause some toxicity, the potent effects of the short fibrillar fragments can be attributed to their ability to spread and replicate *in vivo* and hence to the development of PD-related phenotypes. These results suggest that strategies to reduce the formation and propagation of β-sheet fibrillar species could be an important route for therapeutic intervention in PD and related disorders.

POSTER 39

Climbing fiber-mediated spillover transmission to interneurons is regulated by EAAT4

Shreya Malhotra, Gokulakrishna Banumurthy, Jada H. Vaden, Linda Overstreet-Wadiche, and Jacques I. Wadiche

A single cerebellar climbing fiber (CF) makes hundreds of individual contacts with one Purkinje cell (PC) and releases multiple vesicles at each synapse, a process termed multivesicular release (MVR)[1]. The high synaptic glutamate concentration resulting from MVR is mostly limited to the synaptic cleft by Excitatory Amino Acid Transporters (EAATs) on Bergmann glia that express EAAT1/2 and on PCs that express EAAT4. Nevertheless, sufficient glutamate spills over to activate glutamate receptors on nearby molecular layer interneurons (MLIs) despite the absence of anatomically-defined synaptic specializations. The expression of EAAT4 follows a parasagittal banding pattern and may limit CF-MLI glutamate spillover, similar to its regulation of extrasynaptic neuroglial signaling[2,3]. Here, we use mice expressing Venus under the Aldolase C promoter to visualize EAAT4 expression[4] to test the idea that cerebellar regions are endowed with distinct spillover properties. We made patch-clamp recordings from MLIs and electrically isolated CFs in microzones with both high and low EAAT4 expression. Consistent with our hypothesis, spillover responses are smaller in areas where EAAT4 is expression is high, and larger where EAAT4 expression is low. Because many proteins have patterned expression that matches that of EAAT4, we used the pan-EAAT inhibitor TBOA to block glutamate transporters. The amplitudes of CF-mediated spillover EPSCs onto MLIs were similar between microzones in the presence of TBOA, confirming that these differences resulted from glutamate transport. This suggests that a lower concentration of glutamate escapes from CF-PC synapses when EAAT4 is prevalent. Since spillover signaling to MLIs triggers feedforward inhibition and disinhibition of PCs[5], these results suggest that non-synaptic circuity generates distinct patterns of inhibition in EAAT4 microzones.

1 Wadiche, J. I. *et al. Neuron* **32**, 301-313 (2001).
2 Dehnes, Y. *et al. J.Neurosci.* **18**, 3606-3619 (1998).
3 Tsai, M.-C. *et al. J.Neurosci.* **32**, 1528-1535 (2012).
4 Fujita, H. *et al. PloS one* **9**, e86679 (2014).
5 Coddington, L. T. *et al. Neuron* **78**, 1050-1062 (2013).

POSTER 40

Glycogen synthase kinase 3 (GSK3) inhibition alleviates deficits in *in vivo* spike synchrony, gamma oscillation and cognitive impairment in a schizophrenia mouse model.

Kazuhito Nakao, Robert Hunter, Kiran Sapkota and Kazu Nakazawa

Abstract:
Auditory steady-state responses (ASSRs), tone-evoked EEG oscillations at 40-Hz, is known to be compromised in patients with schizophrenia, although its underlying mechanism and functional outcome is poorly understood. Forty-Hz click train-evoked LFP (local field potential) activity in primary auditory (A1) cortex is also defective in a schizophrenia mutant model (Nakao and Nakazawa, 2014), in which Grin1 gene encoding the indispensable NMDA receptor subunit is deleted in ~50% off cortical and hippocampal GABA neurons in early postnatal development (Ppp1r2cre/Grin1 KO mice). Furthermore, we recently found that immunoreactivity (IR) against phospho-GSK3 (at Y216 in GSK3β), an auto-activated form of GSK3α/β, is augmented in the PV neurons (presumably Grin1-deleted), but not pyramidal neurons, of the mutant mPFC. The IR of GSK3β protein, but not GSK3α, in the PV neurons was also higher in Grin1 mutants. To assess the impact of predictive GSK3β over-activity on the *in vivo* action potential (AP) spike synchrony of cortical pyramidal neurons and *in vivo* tone-evoked LFP gamma oscillation, we took a pharmacological and genetic approach. First, we found that systemic pretreatment of TDZD-8 (nonselective GSK3 inhibitor, 2.5 mg/kg, IP) alleviates in vivo AP spike synchrony deficits (21 pairs, $p = 0.0004$, paired student's t-test) and diminished tone-evoked gamma oscillations in the Grin1 mutant mice (6 channels, $p=0.018$). To determine which isoform of GSK3, GSK3α or GSK3β, elicits the impairment via over-activity, we used the GSK3β-paralog selective inhibitor, BRD3731 (30 mg/kg IP). BRD3731 alleviated the defective gamma oscillation in the Grin1 mutant mice (6 channels, $p=0.009$). To address whether GSK3β-specific inhibition in GABA neurons is sufficient to rescue the mutants' gamma oscillation deficits, we crossed a floxed-GSK3β strain (kindly provided by Dr. J. Woodgett) to the Ppp1r2cre/Grin1 KO mutant mice to generate the GABA neuron-selective GSK3β haploinsufficiency. Preliminary data showed that GSK3β haploinsufficiency reverses the *in vivo* AP spike synchrony deficits ($P = 0.001$, Grin1 KO (24 pairs) vs GSK3β haploinsufficiency (31 pairs), student's t-test). Finally, we assessed whether GSK3 inhibition restored the cognitive dysfunction in the Grin1 mutant mice. TDZD-8 restored the spontaneous alternation in Spatial Y-maze ($n=6$, $p < 0.05$) and paired-pulse inhibition (PPI) of the Grin1 mutant mice ($n=12$, $p=0.05$, two-way ANOVA). These results suggest GSK3β inhibition acting on cortical GABA neurons may ameliorate the cognitive dysfunction in schizophrenia presumably by the restoration of gamma synchronous activity.

Grant Number: **R01 MH110681**

POSTER 41

Cerebral Oxygen Perfusion and Exercise in Aging

Amani M. Norling, Marcas Bamman, Thomas Buford, Jonathan McConathy, Frank Skidmore, Virginia Wadley, Ronald M. Lazar

Abstract:
Higher levels of cardiovascular fitness indexed via maximal oxygen uptake are associated with enhanced physical and cognitive functions. The relationship between fitness and overall function is supported by observed structural changes in the brain. Improvements or maintenance of gray matter volume, white matter integrity, cerebral blood flow (CBF), and improved cognitive functions have been linked to cardiorespiratory fitness. However, research focused on interactions between cardiovascular fitness and changes in cerebral structure and function have not identified the underlying mechanisms of exercise-induced improvements. Several mechanisms underlying exercise-induced improvements have been suggested and include increased neurotrophins and CBF. However, few studies included the effects of exercise on cerebral oxygen utilization. To that end, we propose a study that extends our current understanding by interrogating the effects of exercise on cerebral oxygen utilization.

Poster 42

Noninvasive optogenetics using MRI-guided focused ultrasound delivery of radioluminescent nanoparticles

Megan Rich, Eric Zhang, Katie Burdette, Ashley Dickey, Stephen Foulger, Kelli Cannon, Mark Bolding

Abstract:

The ability to noninvasively activate, silence, and provide receptor subtype specific neuromodulation with high temporal resolution and spatial specificity would greatly advance our ability to study brain circuits in vivo. Optogenetics, the genetic incorporation of light-sensitive proteins such as Channelrhodopsin-2 (ChR2) into target mammalian neurons, has met nearly all of these criteria. However, the essential components of the optogenetic system require invasive procedures with very few non-invasive alternatives. In order to achieve location specific delivery of viral vectors for genetic expression of opsin proteins, invasive surgical infusions are required. Furthermore, the implantation of light emitting fibers deep within brain structures is both technically demanding and causes additional tissue destruction and scarring in target brain regions. Glial scarring at the light source can decrease the effectiveness of light intensities leading to variability in channel activation. In addition, the light intensities required to activate the neurons with fiber optic delivery can result in local heating of the brain tissue, potentially leading to thermal ablation and/or unwanted physiological effects. To overcome these limitations, we are replacing fiber optic implants with light-emitting radioluminscent particles (RLPs) that can be activated non-invasively with X-ray exposure. Here, we report non-invasive delivery of RLPs to target brain regions with MRI-guided focused ultrasound (FUS) blood brain barrier opening (BBBO). In addition, FUS BBBO can be used to deliver viral vectors for light sensitive channel expression. Combined, these components can provide a completely non-invasive optogenetic system.

POSTER 43

Tau-SH3 interactions are critical for amyloid-β toxicity in primary neurons

Jonathan R. Roth, Travis J. Rush, Samantha J. Thompson, Adam R. Aldaher, Jacob S. Mesina, J. Nicholas Cochran, and Erik D. Roberson

Abstract:
The microtubule-associated protein Tau is strongly implicated in Alzheimer's disease (AD) and aggregates into neurofibrillary tangles in AD. Genetic reduction of Tau is protective in several animal models of AD and cell culture models of amyloid-β (Aβ) toxicity, making it an exciting therapeutic target for treating AD. A variety of evidence indicates that Tau's interactions with Fyn kinase and other SH3 domain–containing proteins, which bind to PxxP motifs in Tau's proline-rich domain, may contribute to AD deficits and Aβ toxicity. Thus, we sought to determine if inhibiting Tau-SH3 interactions ameliorates Aβ toxicity. We developed a peptide inhibitor of Tau-SH3 interactions and a proximity ligation assay (PLA)-based target engagement assay. Then, we used membrane trafficking and neurite degeneration assays to determine if inhibiting Tau-SH3 interactions ameliorated Aβ oligomer (Aβo)-induced toxicity in primary hippocampal neurons from rats. We verified that Tau reduction ameliorated Aβo toxicity in neurons. Using PLA, we identified a peptide inhibitor that reduced Tau-SH3 interactions in HEK-293 cells and primary neurons. In primary neurons, endogenous Tau-Fyn interaction was present primarily in neurites and was reduced by the peptide inhibitor, demonstrating target engagement. Reducing Tau-SH3 interactions in neurons ameliorated Aβo toxicity by multiple outcome measures, namely Aβo-induced membrane trafficking dysfunction and neurite degeneration. Our results indicate that Tau-SH3 interactions are critical for Aβo toxicity and that inhibiting them is a promising therapeutic target for AD.

POSTER 44

Diverse mechanisms lead to common dysfunction of striatal cholinergic interneurons in distinct genetic mouse models of dystonia.

Mariangela Scarduzio, Karen L. Eskow Jaunarajs, Michelle E. Ehrlich, Lori L. McMahon, and David G. Standaert

Abstract:

Dystonia is a movement disorder typically resulting in twisted postures via abnormal muscle contraction. Three common forms of isolated human dystonia result from mutations in the *TOR1A* (DYT1), *THAP1* (DYT6), and *GNAL* (DYT25) genes. Experimental models carrying these mutations facilitate identification of possible shared cellular mechanisms of pathophysiology. Clinical and experimental data indicate striatal cholinergic dysfunction in dystonia. Recently, in male *Dyt1*$^{\Delta GAG/+}$ mice (model of DYT1) we reported elevated extracellular striatal acetylcholine by *in vivo* microdialysis and "paradoxical excitation" of cholinergic interneurons (ChIs) in response to dopamine D2 receptor (D2R) agonism by *ex vivo* slice electrophysiology. The paradoxical excitation involved muscarinic receptors (mAChRs) and was caused by a switch in D2R coupling from canonical $G_{i/o}$ to non-canonical □-arrestin signaling. We sought to determine whether these mechanisms in *Dyt1*$^{\Delta GAG/+}$ mice are shared with *Thap1*$^{C54Y/+}$ knock-in and *Gnal*$^{+/-}$ knock-out, respectively DYT1 and DYT6 dystonia mouse models. We found *Thap1*$^{C54Y/+}$ mice of both sexes have elevated extracellular striatal acetylcholine and D2R-induced paradoxical ChI excitation, which was reversed by mAChR inhibition. In contrast, elevated extracellular acetylcholine was absent in male and female *Gnal*$^{+/-}$ mice, but the paradoxical D2R-mediated ChI excitation was retained and only reversed by inhibition of adenosine A_{2A} receptors, not by mAChR inhibition. The $G_{i/o}$-biased D2R agonist failed to increase ChI excitability, suggesting a possible switch in coupling of D2Rs to □-arrestin, as previously seen in *Dyt1*$^{\Delta GAG/+}$. These data show that while elevated extracellular acetylcholine levels are not always detected across all these genetic models of human dystonia, the D2R-mediated paradoxical excitation of ChIs is shared and is caused by altered function of distinct G-protein coupled receptors.

POSTER 45

Retinotopic patterns of structural connectivity between V1 and functional networks

Sara Sims, Utkarsh Pandey, Simone Cedotal, Jennifer Robinson, Kristina Visscher

Abstract:
Vision is an important part of our everyday life, but we use our central vision differently than our peripheral vision. For example, we use central vision to read and peripheral vision when surveying a landscape. Different functions of central and peripheral vision suggest that information from central vision may be processed differently from that in peripheral vision.

A functional connectivity study from our lab suggested that the connections between centrally- and peripherally-representing visual cortex are distinct, and follow well-established networks. Central-representing cortex was preferentially connected to the fronto-parietal (FP) network, mid-peripheral was more connected to the cingulo-opercular (CO) network, and far-peripheral was more connected to the default mode network (DMN).

However, very few studies have examined differential structural connections between central and peripheral representations in early visual areas and functional network regions. In this study, we used diffusion MRI of 786 subjects from the Human Connectome Project (age range=22-36; M/F=335/451). We performed probabilistic tractography on anatomically defined target regions of interest in V1, corresponding to central, mid-peripheral, and far-peripheral visual eccentricities and seed regions of the FP network, CO network, and the DMN. Differences in cortical termination track probabilities were then analyzed on the surface.

Difference maps of pairwise eccentricity comparisons showed the FP network was more connected to far-peripheral than central. The CO network was more connected to mid than central and some regions more connected to mid than far. The DMN was more connected to far than central. These results suggest that eccentricity-based regions are differentially structurally connected to cortical regions within functional network regions. In the comparison of eccentricity-based regions we found resemblance of structural connectivity to functional connectivity network patterns found in a previous study from our lab.

Understanding the differential structural connections of V1 contributes to our understanding of the way the human brain processes visual information and forms a baseline for understanding any modifications in processing that might occur with training, experience, or aging.

POSTER 46

Indirect Dopaminergic Fiber Modulation of Purkinje Cells Through Bergmann Glial Cells in Rett Syndrome Mice

Nash Vador, Wei Li Ph.D., Lucas Pozzo-Miller Ph.D.

Abstract:
Rett Syndrome (RTT) is an autism spectrum disorder categorized by stereotypic hand movements, dyspraxic gait, and dystonia. Dysfunction in the cerebellum may be responsible for these abnormalities, due to RTT commonly involving motor coordination issues. Since dopamine receptors are highly involved in movement, we hypothesize that dysfunctional dopaminergic signaling is responsible for the lack of motor coordination in RTT. Our lab has investigated dopamine receptor 1 (D1), and have learned that it is mainly distributed on Bergmann Glial Cells (BGCs) as opposed to the cerebellum's only neuronal input: Purkinje Cells (PCs). Our goal is to investigate the location of the major dopaminergic inputs to the cerebellum: either the substantia nigra pars compacta (SNc) and/or the locus coeruleus (LC), as well as their role in modulated PCs through BGCs. Through immunohistochemistry in brain sections, we determined that the dopaminergic fibers from the cerebellum partially originate from the SNc. By performing single-molecule fluorescence *in situ hybridization* (smFISH), we learned that D1 receptors are located in BGs as opposed to PCs (which indicated that PCs are indirectly modulated). Future studies involve removal of D1 receptors in the cerebellum of RTT mice, specifically removal of D1 in BGCs, to study the effects on behavior and motor function.

POSTER 47

The Alzheimer's Disease Risk Gene *BIN1* Regulates Neuronal Hyperexcitability

Yuliya Voskobiynyk, Jonathan Roth, J. Nicholas Cochran, Travis Rush, Kelsey Greathouse, Nancy Carullo, Lori McMahon, Jeremy Herskowitz, Jeremy Day, Erik D Roberson

Abstract:
Alzheimer's Disease (AD) affects about five million Americans, who receive only a very modest benefit from current treatment options. Multiple clinical trials have failed in the past, raising interest in identifying new targets to treat AD. Genome wide association studies (GWAS) have identified bridging integrator 1 (*BIN1*) as one of the leading genetic risk factors in AD. Neurons express a unique BIN1 isoform, though the function of this isoform remains unclear and its contribution to AD is critical to investigate. A key question for the role of neuronal BIN1 in AD pathophysiology is whether it has a direct effect on the neuron's primary function – neuronal firing. To address this question, we developed a human neuronal isoform BIN1 vector and evaluated the effects of BIN1 overexpression in primary hippocampal cultures. First, we determined that robust AAV-driven BIN1 overexpression increases spike and burst frequency on multielectrode arrays. Next, we determined that sparse transient transfection-driven BIN1 overexpression increases calcium influx of transfected neurons on calcium imaging of GCaMP6f calcium indicator. In addition, we determined that higher BIN1 levels induced changes in both excitatory and inhibitory synaptic transmission. To investigate the mechanism by which higher BIN1 induces network hyperexcitability, we evaluated the effect of higher BIN1 levels on intrinsic neuronal excitability using whole-cell patch clamp electrophysiology. In addition, we evaluated the effect of higher BIN1 level on both neuronal morphology by determining the complexity of dendritic arbors and spine morphometry. These data show BIN1's important role in regulating neuronal firing and network hyperexcitability and generate fundamental insights about the mechanistic role BIN1 plays in AD.

Carol Barnes, Ph.D.
Director
Evelyn F. McKnight Chair for Learning and Memory in Aging

Lee Ryan, Ph.D.
Associate Director

POSTER 48

Alzheimer's disease fluid biomarkers related gray matter covariance patterns in healthy older adults

Pradyumna Bharadwaj, Jessica Andrews-Hanna, Philip Kuo, Gene Alexander

Abstract:
Biomarkers of Alzheimer's disease (AD) pathology in cerebrospinal fluid (CSF), including Aβ42, pTau181, and the ratio of pTau181/Aβ42, can help identify those with increased risk for dementia, before the onset of clinical symptoms. How these CSF biomarkers relate to regional patterns of gray matter (GM) atrophy in cognitively unimpaired older adults has yet to be fully investigated. Here, we applied a multivariate network analysis technique, the scaled subprofile model (SSM; Alexander & Moeller, 1994) to identify gray matter covariance patterns related to CSF measures of Aβ42, pTau181, and the ratio of pTau181/Aβ42, in a sample of healthy older adults drawn from the Alzheimer's disease Neuroimaging Initiative (ADNI2; N=146; Age=73.5 ± 6.4 years, range=56-89 years; sex (F/M)=76/70; Education= 16.5 ± 2.5 years; MMSE=29.1 ± 1.2; CDR = 0; APOE-ε4 (N/Y)=108/38). GM maps were segmented from 3T T1-weighted volumetric magnetic resonance imaging (MRI) scans with SPM12, spatially normalized using diffeomorphic registration (DARTEL), and smoothed with a Gaussian kernel of 10mm. Regional SSM network analysis was performed on these GM maps using Akaike Information Criteria with 2000 Bootstrap iterations to identify linear combinations of GM patterns associated with each of the three fluid biomarker measures. The pTau181/Aβ42 - related GM SSM pattern (R^2=0.10, p≤ 4.4E-05) was characterized by bilateral reductions in the vicinity of the superior temporal gyrus (STG), and extensive bilateral GM reductions in cerebellar lobules. The pTau181 related GM SSM pattern (R^2=0.06, p≤ 2.75E-03) showed extensive bilateral reductions in the cerebellum extending into the anterior cerebellar lobule. In contrast, CSF Aβ42 did not exhibit an SSM pattern with robust regional GM contributions in this cohort. Additionally, the pTau181/Aβ42 (R^2 change = 0.042, p ≤ 0.007) and pTau181 (R^2 change = 0.042, p ≤ 0.008) related GM patterns each remained significantly associated with their respective CSF biomarker, after adjusting for age, sex, years of education, APOE genotype, hypertension status, and intracranial volume. These results demonstrate that AD-related CSF biomarkers including pTau181 and its ratio to Aβ42 may be associated with individual differences in regional topographies of GM volume, involving temporal and cerebellar brain regions, in healthy cognitively unimpaired older adults. Together, these findings provide further support for the use of CSF fluid biomarkers in evaluating the earliest preclinical effects of AD and their relation to the effects of brain aging.

POSTER 49

Comprehensive phenotyping of patient-derived fibroblasts from patients with sporadic Alzheimer's Disease

Greg Branigan, Lucia Whitman, Mandi J. Corenblum, Lalitha Madhavan, Roberta Diaz Brinton

Abstract:
Globally, neurological disorders rank as the leading cause of disability-adjusted life-years, and the second-leading cause of deaths. The high global prevalence and economic impact of Alzheimer's disease presents a significant public health challenge while the identification of early biomarkers to diagnose Alzheimer's disease (AD) remains a challenge. It has been shown that risk for late-onset AD is partially driven by genetics while studies using pathway analysis have implicated immunity, lipid metabolism, tau binding proteins, amyloid precursor protein (APP) metabolism and mitochondrial energetics as possible mechanisms of disease risk. Given the lack of successful mechanistic studies for AD biomarkers, the Center for Innovation in Brain Science (CIBS) at the University of Arizona has acquired and banked fibroblast lines from male and female patients with sporadic age-associated neurodegenerative diseases (n=12/disease) and age-matched healthy controls. Human dermal fibroblasts (hDF) from patients with Alzheimer's disease (AD) were phenotypically profiled for both genetic (genetic sex, APOE genotype, mitochondrial haplotype) and molecular (transcriptomics, metabolomics, immunological profile, bioenergetic signature and mitochondrial respiration) characteristics to determine inherited, age- and sex-related mechanisms of neurodegeneration. To address morphological and cytochemical phenotypes, hDF lines were stained by IHC for known AD aggregation proteins amyloid-beta and hyperphosphorylated tau and profiled using live in-vivo imaging for mitochondrial tracking. Using this approach, we have begun to establish phenotypic profiles for neurodegeneration in Alzheimer's disease using a patient-specific cell model. We will continue to generate and characterize reprogrammed patient-derived fibroblast and induced neural cells to determine the molecular pathways driving early age-associated AD vulnerability. Preliminary results of comprehensive phenotyping in hDF show a variety of APOE genotypes present in the samples (APOE 2/3, 3/3, 3/4, 4/4) representing a roughly even distribution of genetic sex in each genotype. Preliminary experiments show common markers of aggregations between CNS and peripheral fibroblast indicating opportunities novel biomarker development.

POSTER 50

Age-related, specific changes in expression of several central melanocortin receptor subtypes in the rat

Monica K. Chawla, Marc A. Zempare, Victor J. Hruby, Carol A. Barnes, Minying Ca

Abstract:
The five melanocortin receptors cloned so far (MCR1-5) have been associated with control of inflammatory disorders, immunomodulation, antipyretic effect and prevention of brainstem ischemia and reperfusion injury (Schimolli et al. 2009). It has been reported that the human melanocortin 4 receptor (hMC4R) is involved in neurodegenerative disease (Shen et al., 2016). Melanotropins may protect against the progression of Alzheimer's disease (Giuliani et al., 2014). Furthermore, administration of α-MSH or its more stable analog [Nle^4,$D\text{-}Phe^7$]-α-MSH (NDP-α-MSH) has been observed to enhance learning and memory (Beckwith, et al. 1975). However, the impact of age with respect to melancortin receptor expression remains unexplored. Previously we have shown that the total expression of melanocortin receptor is reduced in the aged rats in four of the six brain regions studied. In the present study, we systematically investigated the expression of 5 different subtypes of melanocortin receptors in brain of young (9 months) and aged (23 months) rats that were assessed for their cognitive status in memory tasks. Spatial memory and visual discrimination ability were assessed using the Morris watermaze task. Six regions of the brain were extracted from each animal, including the frontal cortex + anterior midbrain, parietal cortex, cerebellum, posterior midbrain, hippocampus and occipital lobe. We collected the membrane fragments from each region of all animals in each age group, then ran a specific binding assay using iodine labelled NDP-α-hMCHR1-5 on a high throughput Micro Beta II radiation counter. Six samples were measured from each animal for each region, and then averaged to produce a single count for each animal in each region. All measurements were collected in a blind fashion. We then ran a linear regression analysis with spatial learning behavior and specific receptor binding for hMCHR1-5 receptors using Graph-pad Prizm software. A significant correlation was found between spatial memory and two receptor subtypes MCH-1R ($p = 0.048$) and MCH-3R ($p = 0.049$) in old animals. This finding potentially opens a new window of discovery for exploring and developing new treatments for cognitive changes that arise in normative aging and in neurodegenerative disease.

POSTER 51

A patient iPSC-based platform for investigating idiopathic Parkinson's disease

Mandi J. Corenblum, Anandhan Annadurai, Kanchan Shrestha, Lalitha Madhavan

Abstract:
Human induced pluripotent stem cells (iPSCs) are proving to be a valuable source of patient cells for generating neural phenotypes relevant to Parkinson's disease. Here we compared iPSC-derived midbrain dopamine (DA) neurons derived from the skin fibroblasts of late-onset idiopathic Parkinson's disease (PD) subjects and age-matched controls (AMCs). Specifically, we comparatively analyzed several neurodegeneration relevant aspects including DA neuron survival, differentiation, morphology, mitochondrial function, oxidative stress, and autophagy. Our data indicate that the iPSCs from PD subjects had lower viability rates, and a reduced capacity to generate neurons when induced to differentiate via a floorplate dual SMAD inhibition method. At day 42 post-differentiation, the efficiency of tyrosine hydroxylase positive (TH+) DA neuron generation did not differ between the PD and AMC cultures. However, the morphology of the DA neurons from PD subjects appeared altered in that the cells displayed a smaller soma size, reduced number of neurites, and shorter neurite lengths, compared to AMC cultures. Moreover, PD DA neurons expressed higher levels of reactive oxygen species, and compromised mitochondrial function. In addition, it was found that autophagy was dysregulated in the PD neurons, and was associated with increased protein levels of alpha-synuclein, as compared to AMC cells. Our current studies are further extending these findings by examining the activity profile (electrophysiological and others) of the iPSC-derived DA neurons. In summary, our study develops an iPSC-based neuronal model that captures a phenotype relevant to the study of idiopathic PD, as well as biomarker and therapeutic testing.

POSTER 52

Spatial eye-blink learning but not age predicts theta-gamma coupling in the CA1 region of the hippocampus

Lindsey M. Crown, Daniel T. Gray, Lesley A. Schimanski, Carol A. Barnes, Stephen L Cowen

Abstract:

Cross-frequency coupling (CFC) between theta- and gamma-band activity in the hippocampus has been linked to memory encoding and retrieval. Recent data suggest that the frequency of the gamma-band component of theta-gamma CFC differs as the relative contribution of entorhinal or hippocampal CA3 drive to mnemonic circuits within CA1 changes. While there are differing interpretations with respect to the generation of low gamma (25 - 50 Hz), one hypothesis is that it reflects drive from CA3 to CA1 while high gamma (75 - 90 Hz) denotes drive from medial entorhinal cortex (MEC) to CA1 (Colgin et al., 2009). Little is known about how activity in these frequency bands and their coupling changes with age; however, there are fewer functional Schaffer collateral synapses onto CA1 pyramidal cells and CA3 pyramidal cells show increased excitability. Given such alterations in these network properties, we hypothesized that high-gamma CFC associated with entorhinal input would be greater in aged animals. To examine this question, local field potential activity of 12 rats (n = 6 young, 9-12 mo, n = 6 old, 25-28 mo) was analyzed as they performed a spatial eye-blink conditioning task (Schimanski et al., 2013). We measured low-gamma power, high-gamma power, and theta-gamma phase-amplitude coupling (PAC) as animals approached and departed from the region of the maze associated with a brief eyelid stimulation. We observed no difference between young and old animals in 1) peak gamma frequency, 2) in CFC, or 3) the ratio of low- to high-gamma power. Interestingly, we observed that animals that did not develop reliable eye blink conditioning (n = 5), regardless of their age, showed greater low-gamma relative to high-gamma power than those (n = 7) that did consistently show conditioning (two-sample t-test, $p = 0.01$). This effect was apparent after 5 days of training, suggesting that eye blink training altered the relative contribution of entorhinal drive to CA1. In addition, low-gamma PAC, but not high-gamma PAC, recorded as animals approached the eye-shock zone, was positively correlated with eye-blink learning in those animals that learned the task (one-sample t-test, $p < 0.01$), but not in animals that did not display learning, regardless of age. Taken together, these results suggest that age is a less important predictor of CA1 theta/gamma dynamics than is performance.

POSTER 53

RNA stress granule components are dynamically expressed during aging and stress conditions in rats and fruit flies

Randall Eck, Monica K. Chawla, Bhavani Bagevalu Siddegowda, Natalie J. Carey, Marc A. Zempare, Christie J. Nguyen, Dean Billheimer, Carol A. Barnes, Daniela C. Zarnescu

Abstract:

During times of cellular insult, non-membrane bound organelles called RNA stress granules form to sequester mRNAs, translation initiation factors and proteins into dense cytoplasmic structures, halting translation. Dysfunction in the dynamic assembly and disassembly of RNA SGs has been linked mechanistically to age-related neurodegenerative diseases. It is not known, however, how these mechanisms are affected during aging. To understand the molecular mechanisms that underly these links, we profiled the dynamic changes of RNA SGs during aging and their relationship to stress resiliency through examining the expression of genes critical to translation initiation and RNA SGs formation in behaviorally characterized young (6-10 mo, n=11), middle-aged (15-19 mo, n=11), and old rats (23-25 mo, n=13). These rats were assessed for their spatial memory, working memory, and motor function using the Morris water maze. Some of the genes profiled were G3BP1, necessary for RNA SGs formation, FMRP, a modulator of mRNA association with RNA SGs, EIF2alpha, a translation initiation factor whose phosphorylation indicates RNA SG formation, and PABP and TIAR among others. Western blots and real-time PCR found region-specific expression of these critical genes in the hippocampus, pre-frontal cortex, and cerebellum throughout aging. Using regression models, we sought to determine if these region-specific expression changes can account for variation among rats in behavioral performance, when taking age into account. We used Principle Component Analysis to determine if the variations among critical protein and transcript expression levels reveal differences or similarities between rats that relate to age or behavioral performance. The levels of key proteins and transcripts, along with other analysis trends, will be compared between young and old rats who received maximum electro-convulsive shock treatment (shock duration = 1 second, current intensity = 85mA, 1 hour recovery) and those who did not. In fruit flies, the dynamic response of RNA SGs under stress conditions appears to vary with age compared to the non-stressed control condition. Future investigation will focus on isolating RNA SGs from fruit flies to examine how components associated with RNA/protein structures change during aging and in response to multiple stress conditions.

POSTER 54

Perineuronal nets in the cerebral cortex of cognitively-assessed aged macaque monkeys

Daniel T. Gray, Wonn Pyon, Nicole De La Peña, Rachel Schwyhart, Emma Wallace, Joana Puchta, Wolfgang Härtig, Carol A Barnes

Abstract:
Perineuronal nets (PNNs) are specialized extracellular matrix structures that envelop specific neurons in the central nervous system and play critical roles in controlling plasticity and maintaining syn aptic function (Sorg et al., 2016, J Neurosci). Alterations in the expression of different components of the extracellular matrix have been shown to occur in normative brain aging, as well as in several nervous system disorders. No studies have investigated PNNs across the lifespan of behaviorally characterized, aged nonhuman primates. Furthermore, the impact that potentially altered PNNs have on the manifestation of different aspects of age-associated cognitive decline is not clear. To these ends, the present study used fluorescence labeling and unbiased quantification of perineuronal net markers [*Wisteria floribunda* agglutinin (WFA) and the chondroitin sulfate proteoglycan aggrecan] on the brains from a colony of 30 rhesus macaque monkeys ranging in age from 7 to 32 years. All of these monkeys also underwent tests of spatial short-term memory (delayed response), object recognition memory (delayed nonmatching-to-sample), and object discrimination, which allowed relationships between PNNs and cognition to be investigated. While there are interesting trends with respect to age, PNNs and parvalbumin (PV)-immunoreactive neurons, our preliminary results (N = 3 aged, mean 28 years; N = 3 adult, mean 11 years) suggest no age effect. The data do suggest that the strongest associations are found between the proportion of PV-immunopositive neurons with nets and behavior. Specifically, animals with more perineuronal nets surrounding PV-immunoreactive neurons tended to show worse behavior on all of our cognitive tasks. Furthermore, animals that exhibited fewer PNNs associated with PV-immunopositive cells tended to show better behavioral performance on our tasks. We are currently expanding the sample size, PNN markers, and the brain regions analyzed to more thoroughly characterize these nets across aging.

POSTER 55

A computational model of aged head direction network updating in the presence of sudden spatial cue mismatch

Adam W. Lester, Adele J. Kapellusch, Carol A. Barnes

Abstract:
As with older adults, aged rats show pronounced impairments on a number of different spatial navigation tasks as well as a bias toward relying on self-motion (i.e., idiothetic) over environmental (i.e., allothetic) cue-based navigation strategies (Lester et al., 2017). Rosenzweig et al. (2003) found that, when exposed to conflicting allothetic and idiothetic feedback, aged rats were impaired in navigating to an allothetic cue-aligned goal location and the place cell networks of aged rats were delayed in realigning their firing fields to match the spatial information relayed by the allothetic cues. The Instantaneous Cue Rotation (ICR) task used here requires animals to navigate to a reward location that is always aligned to the projected visual cues in the environment (Lester et al., 2018). We previously reported that, when young and aged rats were tested on the ICR task, allothetic cues were found to exert a less pronounced influence on the running behavior of aged rats following sudden cue rotation. The overall pattern for young rats, in contrast, suggested a reliable although incomplete control by allothetic cues, which may reflect a greater tendency for young animals to resolve conflicting allothetic-idiothetic feedback by integrating information from both. A continuous attractor neural network model was created to assess how a sudden rotation of visual cues may affect the spatial tuning of head direction cell networks and how the behavior of these networks may be altered in the presence of erroneous self-motion feedback (i.e., idiothetic error). The model incorporates a head direction (HD) and angular head velocity (AHV) network, the tuning of which depend on both angular movement and visual cue inputs. In the absence of any idiothetic error, the HD and AHV networks collectively undergo a gradual but reliable realignment of their directional firing after visual cue rotation. In contrast, the introduction of idiothetic errors either amplifies or diminishes visual cue control over HD-AHV alignment depending on the degree and direction of drift these errors induce in the network's directional firing. As a consequence, visual cues exert less reliable control over directional tuning and often lose control over the networks directional tuning following visual cue rotation. Considered in the context of known age-related changes in vestibular function as well as deficits in self-motion perception and path integration, the findings from this computational model suggest a plausible mechanism that could contribute to impaired integration of conflicting spatial signals in aged spatial networks

POSTER 56

Interactive effects of sex and BDNF Val66Met polymorphism on cognition in older adults

Stephanie Matijevic, Max Elias, Matthew J Huentelman, Lee Ryan

Abstract:
Brain-derived neurotrophic factor (BDNF) promotes synaptogenesis and neurogenesis, and may play a critical role in supporting plasticity mechanisms underlying hippocampal-dependent memory. The BDNF gene Val66Met polymorphism contributes to individual variation in BDNF secretion, as carriers of the Met allele have abnormally reduced BDNF levels. Consequently, the Met allele has been shown to negatively influence hippocampal function, and in turn, episodic memory. This has implications for cognitive aging, given the susceptibility of the hippocampus to age-related damage and dysfunction. Indeed, the Met allele has been linked to enhanced memory deficits in older adults. To a lesser degree, BDNF has been implicated in the relationship between age and other cognitive domains, such as executive functioning. Evidence from the animal literature indicates that BDNF protein expression may differ by sex, as estrogen appears to regulate BDNF expression in the brain. Sex may therefore moderate the relationship between the Met allele and cognitive performance. The present study thus aims to characterize how the interactions between age, sex and the BDNF Met allele affect memory and executive function performance in older adults.

Neuropsychological testing and genotyping was carried out for 268 cognitively normal older adults (mean age = 72.27, ages 60-90). Participants with a BDNF Met/Met or Val/Met genotype were classified as Met allele carriers. Memory and executive function composite scores were calculated from the neuropsychological test data (Glisky & Kong, 2008). Univariate GLMs were run to assess interactions and main effects of age, sex and BDNF Met carrier status on the composite scores.

For the memory composite scores, significant effects were found for Age ($F = 22.73$, $p < 0.001$), Sex ($F = 36.32$, $p < 0.001$), and the three way interaction between Sex, Carrier status, and Age ($F = 5.038$, $p = 0.026$). Females scored higher than males. While this difference increased with age among the Met non-carriers, it lessened among the carriers, as the memory composite scores negatively correlated with age only in the carrier females and non-carrier males. For the executive function scores, the effects of Age ($F = 9.95$, $p = 0.002$) and Sex x Carrier status interaction ($F = 6.61$, $p = 0.011$) were statistically significant. Male carriers performed better than both non-carrier males and carrier females. BDNF carrier status is shown to interact with sex to influence both memory and executive function performance. These results suggest that the presence of the met allele may be less detrimental for males than for females, and perhaps even beneficial in regards to executive functioning.

POSTER 57

The immuno-metabolic crisis in the aging female brain: Implications for Alzheimer's disease

Aarti Mishra, Yuan Shang, Yiwei Wang, Fei Yin, Roberta Diaz Brinton

Abstract:
Alzheimer's disease (AD) is characterized by a long latent prodromal stage with recent discoveries pointing to the perimenopausal transition in women as a "tipping point" in the development of the AD phenotype (Brinton et al., 2015). The hallmark chronic low-grade inflammation in both aging and menopause has been implicated as a unifying factor that bridges across AD risk factors (Mishra and Brinton, 2018). Yet, the endocrine state specific effect of neuroinflammation on female aging has not been characterized. In this study, we characterize the neuroinflammatory profile across chronological and endocrine aging transitions and establish its relevance to AD and neurodegenerative inflammatory mechanisms. Preliminary findings from the perimenopausal rat model, in which we can experimentally segregate the effects of chronological aging from endocrine aging, indicate that the inflammatory phenotype is quite dynamic throughout the endocrine transition in menopause, Our results show that type I and type II interferon (IFN) response genes, recently implicated in age related neurodegeneration (Mathys et al., 2017) are upregulated in the hippocampus the perimenopausal transition. Co-incident with the upregulation of the IFN response genes in the hippocampus, was the overexpression of major histocompatibility complex (MHC)-II genes in white matter tracts – corpus callosum and fimbria. Reproductive irregularity also affected phagocytic response and redox status of microglial cells. Endocrine aging was associated with shifts in mitochondrial function in astrocytes and microglia. Estradiol regulation of the upregulation of interferon response genes was validated by ovariectomy and the estradiol prevention paradigm rescued the neuroinflammatory phenotype. Clinical microarray data from the hippocampus was also analyzed to accomplish translational validity of the findings and, establish if the upregulation of MHC-II was preferentially observed in females. The characterization of inflammation in the female aging brain and its role in transition to AD vulnerability has, thus far, been scarce. This pioneering study elucidates the dynamic immune profile in brain that occurs during chronological and endocrinological aging, which is coincident with decline in steroid hormones and brain glucose metabolism. Molecular characterization of the neuroinflammatory mechanisms during this neuro-endocrine transition state can inform therapeutic strategies to mitigate the risk of onset of Alzheimer's disease in women.

POSTER 58

Context-dependent memory in cognitively-normal older e4 carriers and non-carriers

Justin M Palmer, Ashley V Lawrence, Matthew D Grilli, Matthew J Huentelman, Joshua S Talboom, Lee Ryan

Abstract:
The ability to distinguish between highly similar objects requires the use of pattern separation or orthogonalizing information into distinct representations in the brain. Older adults generally perform worse on pattern separation tasks compared to younger adults by incorrectly identifying similar objects as ones seen previously. This suggests that older adults may have a decreased ability to create distinctive representations for objects with many overlapping features compared to younger adults. Context plays an integral role in recognition memory for objects, and the context in which an object is viewed can lead older adults to make even more similarity judgement errors. Older adults are more likely to make pattern separation errors (falsely recognizing similar objects as "old") when these similar objects are embedded in a context that was previously seen. Age-related impairment in pattern separation may therefore be a combination of a lack of utilizing details along with an over-reliance on the familiarity of the context in which an object is placed. Evidence suggests that changes in perirhinal cortex may be the neural mechanism underlying older adults' bias toward context familiarity. In contrast, preliminary data from our laboratory suggest that older adults who carry the APOE e4 allele are less likely to be influenced by the scene context during object recognition compared to older noncarriers. The e4 allele may confer a memory benefit that moderates older adults' susceptibility to rely on contextual familiarity, rather than object details. Participants were recruited from an existing pool in our laboratory. Older adults were carefully screened to exclude cognitive impairment. APOE status was determined from saliva by the Translational Genomics Institute in Phoenix, Arizona. Objects were embedded in semantically-related scenes and presented one at a time. Participants indicated whether each presented object was "new", "similar", or "different" compared to objects seen previously. Each object was either embedded in a context that was seen previously, a new context that had not been seen before, or on a white background. Behavioral performance was compared between e4 carriers and noncarriers. Our results indicate that carriers and noncarriers do not differ on traditional recognition performance. However, consistent with our preliminary data, older e4 carriers were less susceptible to the influence of repeated contexts. The results suggest that the presence of the e4 allele may provide a memory benefit to older adults because carriers may not be biased toward relying on the scene context.

POSTER 59

Quantification of neuronal and astrocytic cells in the locus coeruleus of cognitively assessed, young and aged nonhuman primates

Wonn S. Pyon, Daniel T. Gray, Rachel E. Schwyhart, Emma G. Wallace, Nicole de la Peña, Carol A. Barnes

Abstract:
The locus coeruleus is a small brainstem nucleus that is known for its role in supplying noradrenaline to various regions in the brain. The locus coeruleus is especially susceptible to age-related neurodegeneration and is one of the first regions to display Alzheimer's and Parkinson's pathologies (Mather and Harley, 2016), in part due to its high bioenergetic need. Whether differences in number of tyrosine hydroxylase (TH)-expressing neurons significantly contribute to age-related cognitive decline remains less clear. To investigate this, coronal brainstem sections from cognitively assessed rhesus macaques (N = 3 aged, mean 28 years; N = 3 adult, mean 11 years) were immunohistochemically labelled to visualize neuronal nuclei (NeuN), catecholaminergic neurons (TH), astrocytes (glial fibrillary acidic protein – GFAP) and vasculature (*Solanum tuberosum* lectin – STL). For this study, unbiased stereological techniques are used to quantify neuronal numbers. Astrocyte and vascular characteristics are also investigated. The preliminary results suggest a trend towards lower TH neuron density within the locus coeruleus of aged monkeys. There was also a trend for a relationship between higher TH density and better object recognition memory (delayed nonmatching-to-sample) performance. This trend was not observed with performance on spatial short-term memory (delayed response) or object discrimination tasks. We are currently examining whether the volume of vasculature within the sampled region, or if properties of astrocytes within the region differ with age. Additionally, we are expanding the number of animals, assessing other neuronal cell types, and evaluating stereological estimates of volume to more thoroughly characterize age-related changes in the locus coeruleus.

POSTER 60

Role of prefrontal-hippocampal interactions in age-related deficits in spatial working memory

Sahana V. Srivathsa, Salma O. Khattab, Adam W. Lester, Carol A. Barnes

Abstract:

Neural ensembles in hippocampus and mPFC play a crucial role in memory-guided navigation and decision making, a process susceptible to decline with age in mammals. These regions are connected via a unidirectional projection from the ventral hippocampus to the mPFC and damage or inhibition of this circuit leads to impairments in spatial alternation tasks (Wang et al, 2006). Rats with mPFC lesions show an impairment on spatial working memory tasks (Kim et al., 2009). On the other hand, rats with hippocampal lesions are impaired in both the spatial localization and spatial working memory components (Sapiurka et al., 2016). One task that was developed to test the interactions between these regions is a continuous spatial alternation task (Frank et al., 2000), which consists of two interleaved components: an “outbound” component (working memory) and an “inbound” component (spatial memory). Behavioral data from young (9-15 mo) and old (23-30 mo) rats tested on this task reveals that aged rats are slower in learning the inbound component and are unable to learn the outbound component (Kapellusch et al., 2018). The outbound component of the task requires coordination between the hippocampus and mPFC, suggesting that these interactions are impaired in aged rats. Here, we report data from an ongoing experiment studying the age-associated changes in the hippocampal-mPFC circuit that underlie the behavioral decline in spatial alternation in aged rats through simultaneous electrophysiological recordings in the ventral CA1 region of the hippocampus and in the dorsal ACC region of the mPFC. As disruption of hippocampal SWRs during awake rest leads to impairment of working memory performance (Jadhav et al., 2012) and CA1-mPFC synchronization is stronger during awake SWRs and enhanced in early stages of learning (Tang et al., 2017), several predictions of impact of age on these circuits can be offered. First, there may be a decrease in the synchronization between CA1 and mPFC unit activity during behavior in aged rats compared to young rats. This is likely to show a strong correlation with the age-related impairments in learning the outbound component. Second, since co-occurrence of hippocampal SWRs and spindles in the mPFC during sleep has been implicated in memory consolidation (Maingret et al., 2016), examining this relationship may provide insights into changes in memory consolidation with age. Furthermore, as increased coupling of the hippocampus and mPFC to the theta and gamma bands is correlated with spatial working memory (Jones et al., 2005; Tamura et al., 2017), we will study the disparities in this coupling during the working memory epochs of the task, between the age groups.

POSTER 61

Web-based study of forty-one thousand women reveals factors associated to cognitive enhancement during menopause

Joshua S Talboom, Asta K Haberg, Matthew D. DeBoth, Marcus A Naymik, Isabelle Schrauwen, Candace R Lewis, Ashley L Siniard, Stacy F Bertinelli, Callie Hammersland, Amanda J Myers, Meredith Hay, Carol A Barnes, Elizabeth Glisky, Lee Ryan, Matthew D Huentelman

Abstract:
Recently, our web-based cognitive study of over 75,000 individuals between the ages of 18-85 (www.mindcrowd.org) revealed that women's paired associates learning (PAL) performance was significantly higher at the fifth decade of life. Coinciding with this timepoint in a woman's life is menopause, marked by a cessation of ovarian hormones. Numerous studies have linked ovarian hormones and their cessation at menopause to cognitive changes in women. To evaluate potential links between menopause and cognition in our cohort, we developed a ten question menopause survey. Survey questions asked women about their contraceptive and hormone therapy use as well as if they had undergone an oophorectomy or hysterectomy. To date, over 7,130 women have completed the survey. We found the number of years that women reported using contraception was significantly associated with lower PAL performance (b=-0.034 word pairs/year of contraception, p=0.017). This effect was found after controlling for age, education, and several other factors related to PAL performance. This finding is in line with prior animal work linking contraception exposure to lower cognitive performance. This study helps further bridge the gap between animal and human studies and highlights the translational impact of contraception on cognition.

POSTER 62

Mediation of age and hippocampal volume by temporal lobe white matter hyperintensities differ in relation to APOE e4 status in healthy older adults.

Emily Van Etten, Pradyumna Bharadwaj, Georg Hishaw, Theodore Trouard, Gene Alexander

Abstract:
While white matter hyperintensities (WMH) have been associated with hippocampal atrophy, less is known about how the regional distribution of WMH may differentially affect hippocampal volumes in healthy aging. Apolipoprotein E (APOE) ε4 carriers may be at an increased risk for WMH and greater hippocampal atrophy. The present study sought to investigate whether regional WMH mediate the relationship between age and hippocampal volume and whether this relationship is moderated by APOE ε4 status in healthy aging. A cohort of healthy adults (n=192, 94F/98M, mean±sd age=70.5±10.1, mean±sd Mini-Mental State Exam=29±1.2, APOE ε4 status (yes/no) = 59/133), 50 to 89 years of age were included. T1 weighted 3T volumetric MRIs were obtained and processed using Freesurfer (v5.3) software to obtain hippocampal volumes averaged across hemispheres. WMH in the four cerebral lobes were computed using T1 and T2 FLAIR scans and a lesion segmentation toolbox (Schmidt et al., 2012) with Statistical Parametric Mapping (SPM12). Total intracranial volume was computed for each participant using SPM12 to adjust hippocampal and WMH volumes for differences in head size. Mediation analyses were conducted with PROCESS macro software (Hayes, 2012) on SPSS, using bootstrap resampling with 10,000 iterations to produce bias corrected 95% confidence intervals. Temporal lobe WMH significantly mediated the relationship between age and average hippocampal volume, and this effect was moderated by APOE ε4 status (-.02 (SE=.01), 95% CI, [-.04, -.003]. APOE ε4 carriers, but not non-carriers, showed negative indirect effects of age on hippocampal volume through temporal lobe WMH (APOE ε4 carrier: -.02 (SE=.01), 95% CI, [-.03, -.003]; APOE ε4 non-carrier: .00 (SE=.01), 95% CI, [-.01, .02]). These findings remained significant after additionally adjusting for sex, years of education, and hypertension status. There were no significant mediation effects for frontal, parietal, and occipital lobe WMH, with or without covariates. The results indicate that the effects of aging on hippocampal volume are mediated by WMH regionally localized to the temporal lobes and that this effect depends on APOE ε4 carrier status. Together, these findings suggest that differences in hippocampal volumes observed in the context of healthy aging may be in part related to the influence of APOE ε4 on WMH and associated vascular mechanisms. Further research is needed to evaluate how regional WMH may influence other neuroanatomical effects of brain and cognitive aging.

POSTER 63

Dynamic metabolic aging of the female brain during endocrinological and chronological aging

Yiwei Wang, Yuan Shang, Aarti Mishra, Eliza Bacon, Fei Yin, Roberta Diaz Brinton

Abstract:
Natural aging and the perimenopausal transition are associated with brain glucose hypometabolism and mitochondrial dysfunction in females. The bioenergetic crisis is also a hallmark of late-onset Alzheimer's disease (LOAD). Comprehensive understanding of the dynamic metabolic aging process in the female brain can shed light on potential prevention and interventions windows of opportunities to promote healthy aging. Using a rat model recapitulating fundamental characteristics of human menopausal transition, we observed systematic bioenergetic dysregulation in the aging female brain, as well as alternations in key metabolic regulators. Using an unbiased, discovery-based metabolomic and lipidomic approach, we characterized the dynamic adaptation of aging female brain from glucose centric to utilization alternative fuel sources including amino acids, fatty acids, lipids, and ketone bodies, and finally to anaerobic glycolysis, during endocrinological and chronological aging. Transcriptomic profiling of bioenergetic gene networks were consistent with the metabolomic profiles. These data provide the first detailed metabolic profile of the female brain across both endocrinological and chronological aging transitions.

POSTER 64

Effects of induced hypertension in middle aged CYP1A1-REN2 transgenic rats

Marc Zempare, Natalie J. Carey, Amy Dalmendray, Kimberly Young, Kimberly M. Bohne, Loi Do, Theodore Trouard, Kenneth D. Mitchell, Monica K. Chawla, Matthew J. Huentelman, Carol A. Barnes

Abstract:

Hypertension is associated with an increased risk of cardiovascular disease (CVD) and cognitive decline in aging humans (Keenan et al., 2011) with the onset occurring around middle-age (Wilkie et al., 1971). While prior research has suggested an association between CVD and cognitive decline in the elderly (Haring et al., 2013), it is also critical to investigate how this dynamic may evolve from middle to older age. In this study, Cyp1a1-Ren2 xenobiotic-inducible transgenic rats were used to model the gradual rate and age-ofonset observed in humans. In these transgenic rats, Ren2 expression in the kidney is driven by the Cyp1a1 promoter, which is activated by ingestion of indole-3-carbinol (I3C), causing elevated kidney angiotensin levels, increased arterial pressure, and reduced renal hemodynamics (Mitchell et al., 2006). Fifteen month old male rats were assigned to either control or treatment diet groups, and given a battery of behavior tests to establish baseline cognition measures. Following these tests the treatment group received a diet with 0.015% I3C while control rats received a global 18% protein rodent diet. Post-treatment, the same behavioral battery was given to assess the effect of hypertension on cognition. Gradual onset of hypertension was confirmed through systolic and diastolic blood pressure changes. Postmortem heart and kidney analysis replicated and expanded on recent studies (Willeman et al., 2019). The behavioral battery includes spatial and cued versions of the Morris watermaze, spontaneous object recognition (SOR) and a delayed matching- to-place working memory task. Analysis of the hippocampal-dependent spatial watermaze, the perirhinal cortex-dependent SOR, and the prefrontal cortex-dependent working memory task, suggest that these hypertensive rats maintain high performance levels on each behavioral task. While the treated group in this study did show significant cardiac and renal end organ damage as in the Willeman et al. (2019) study, we did not replicate the impairment observed in spatial memory in this larger cohort. Further studies, including those that assess vascular damage in relevant brain regions, are needed to determine if the molecular and cellular changes observed in these animals are similar to those seen in the peripheral vasculature. For example, the persistence of normal cognition after hypertension may be due to compensatory mechanisms such as local modulation of vascular tone and arteriole diameter by neurons and glial cells.

INTER-INSTITUTIONAL

McKNIGHT BRAIN AGING REGISTRY

The Evelyn F. McKnight Brain Institute
University of Alabama at Birmingham

The Evelyn F. McKnight Brain Institute
University of Arizona

The Evelyn F. & William L. McKnight Brain Institute
University of Florida

The Evelyn F.McKnight Brain Institute
University of Miami

POSTER 65

Characterizing the Healthy Oldest Old: The McKnight Brain Aging Registry

Authors: This is a team effort by the McKnight Brain Aging Registry Investigators and Collaborators

Institutions: Evelyn F McKnight Brain Institute, University of Alabama, Birmingham; Evelyn F. McKnight Brain Institute, University of Arizona; Evelyn F. McKnight Brain Institute, University of Florida; Evelyn F. McKnight Brain Institute, University of Miami

Abstract:

The McKnight Brain Aging Registry was initiated to understand and characterize cognitively healthy older individuals over the age of 85 years. This goal is essential to developing strategies to help people retain cognitive health throughout old age. Secondary aims were to develop standardized, reproducible data acquisition methods that could be applied to the current samples as well as other groups for comparison, as well as to develop a cohort of participants and a network of research sites across the McKnight Brain Institutes to employ these methods. Our four sites have worked collectively to achieve these aims. Several other posters in this session will present specific research questions accompanied by results based on this comprehensive dataset. The goal of the current poster is to outline the rich datasets we have collected and describe how these data have laid the necessary groundwork for future studies.

The McKnight Brain Aging Registry has supported the standardization and dissemination of these reproducible methods at multiple McKnight Brain Research Foundation sites. The results of this effort will be of use to all groups studying healthy aging in the oldest old, and the standardization and collaboration across sites has already facilitated NIH funding for multisite studies of healthy aging, and will continue to do so.

We collect several types of data in service of our goals: Demographic and anthropometric data, Vascular risk factors, MRI, Behavioral, Neuropsychological, and Blood biospecimens. These different data modalities have laid the foundation for deep phenotyping of individuals and detailed comparison of how interactions between these factors relate to one another.

The McKnight Brain Aging Registry is a collaborative research study between the four MBRF Institutions (University of Arizona, University of Florida, University of Alabama, Birmingham, and University of Miami). We plan to enroll 200 individuals in the Registry. At the time of this abstract, we have enrolled over 165 participants across the four sites, and have collected complete multimodal datasets from over 130 participants.

Together, these data provide a unique evaluation of the neurocognitive and physiological characteristics of a diverse and representative sample of cognitively unimpaired adults 85+, can be compared to other samples, while supporting collaborative NIH multisite research. These data give critical insights into profiles of risk and protection associated with healthy aging. This presentation describes the available datasets, helping to facilitate future collaborations across MBRF sites to enhance our understanding of successful cognitive aging.

Poster 66

Age related decreases in cortical GABA concentrations assessed over the lifespan abate in cognitively intact adults over 85 years of age

Porges EC, Jensen G, Bharadwaj PK, Franchetti MK, Sims SA, Rezaei RF, Forbes MA, Merritt S, Jessup CJ, Raichlen DA, Geldmacher D, Hishaw GA, Alperin N, Trouard TP, Wadley VG, Levin BE, Woods AJ, Rundek T, Visscher KM, Cohen RA, Alexander GE, Foster BM, Puts NAJ

Abstract:
Edited magnetic resonance spectroscopy (MRS) allows for non-invasive measurement of GABA, the principal inhibitory neurotransmitter. Prior work has demonstrated an age-associated decrease of cortical GABA concentrations during adulthood. In childhood developmental cohorts an age-related increase has been reported, and in midlife no association was found. Further, no study of cortical GABA levels across the lifespan has been reported. Additionally, it is unknown if these previously reported age-related decreases in cortical GABA continue in the cognitively intact oldest old (85 years and older). To generate a more complete understanding of the lifespan trajectory of cortical GABA including the oldest old, we employed metanalytic techniques to extract data points from all published reports of edited MRS of GABA in human cortex. Analyses were limited to publications where figures contained either water or creatine ratios of GABA, and the age of participants with individual data points present. Data were extracted using WebPlotDigitizer from five peer reviewed manuscripts that met these requirements. In addition, two datasets were contributed by collaborators on this project from their previous data collections, and one new data set collected in the oldest-old (n=55 community-dwelling, cognitively unimpaired older adults, ages 85 to 99 [mean ± sd age = 88.1±3.2; M/F = 18/35; mean ± sd MoCA = 25.1±2.4]). These oldest old participants were recruited as part of the McKnight Brain Aging Registry, and MRS of GABA was collected in a midline-frontal lobe voxel (27cm3) on 3T MRIs across the four McKnight Brain Institutes.

The 8 datasets were merged using a Bayesian approach. Each data set was given its own scaling factor, and these parameters were estimated simultaneously with regression parameters using the Stan programming language.
The merged dataset provides evidence for a lifespan trajectory of cortical GABA that is consistent with Log-normal distribution. Of note, when those 85 and older are explored independently from the aggregated lifespan data, there was no age-related decrease. When incorporated into the lifespan model, the oldest old are well predicted by the gradual attenuation characteristic of the far-right tail of the log-normal model. The compiled data, comprised of 739 participants between 8-99 years, provide the first illustration of cortical GABA concentrations throughout the lifespan. Taken together these data present a coherent log-normal shape with an early life increase, mid-life stability, decrease during aging, and an abatement of this decrease in those over 85 who remain cognitively intact.

POSTER 67

Relation of daily activity patterns to cortical gray matter maps in the healthy oldest old: Findings from the McKnight Brain Aging Registry.

David Raichlen, Pradyumna Bharadwaj, Mary Franchetti, Sara Sims, Roxanne Rezaei, Suzanne Merritt, Cortney Jessup, Eric Porges, David Geldmacher, Georg Hishaw, Noam Alperin, Theodore Trouard, Virginia Wadley, Bonnie Levin, Adam Woods, Tatjana Rundek, Kristina Visscher, Ronald Cohen, Gene Alexander

Abstract:
Engaging in increasing levels of physical daily activity (PA), while having good sleep quality may help in maintaining cognitive and brain health during aging. Wrist-worn accelerometers provide a way to measure engagement in different aspects of daily activity, including levels of moderate to vigorous physical activity (MVPA), fractal patterns of consistent PA (FPA), as well as movement during sleep, reflecting sleep efficiency (SE). How these different measures of activity relate to brain health in oldest old adults has yet to be investigated. We sought to determine whether having high levels of MVPA, FPA, and SE are associated with greater cortical gray matter in a cohort of oldest-old adults from the McKnight Brain Aging Registry. For this analysis, 64 community-dwelling, cognitively unimpaired older adults, ages 85 to 99 were included [mean±sd age = 87.9±3.3; M/F = 31/33; mean±sd Mini-Mental State Exam = 28.4±1.3]. Volumetric T1-weighted 3T MRI scans were acquired across the McKnight Brain Institutes at the University of Arizona, University of Alabama at Birmingham, University of Miami, and University of Florida - Gainesville. The MRI scans were processed using Freesurfer (v6.0) and total intracranial volume (TIV) was computed using SPM12 to adjust vertex-wise volume maps for head-size. Measures of MVPA, FPA, and SE were acquired with Actigraph accelerometers worn on the non-dominant wrist for up to seven consecutive days. MVPA, FPA, and SE were defined with standard algorithms using the GGIR package (v1.6.0) in R (v3.4.4). Analyses tested the relation of MVPA, FPA, and SE to cortical maps of thickness, area, and volume using extent thresholds to maintain an overall $p<0.05$ false positive rate (Greve & Fischl, 2018). Results showed that, after adjusting for TIV, higher levels of MVPA were significantly associated with increased volumes in the vicinity of left lateral temporal and medial frontal regions. Greater MVPA was also significantly associated with greater cortical thickness in parieto-occipital regions; greater FPA was associated with greater thickness in precentral and inferior parietal regions; and greater SE was associated with increased cortical area in inferior parietal regions. The regions of cortical volume, area, and thickness were also significantly associated with better cognitive performance. Among cognitively unimpaired oldest old adults, engaging in more MVPA and FPA, and having better SE are each associated with enhanced gray matter, involving brain regions that are related to better cognitive functions. Together these results support the benefits of PA and sleep quality for brain health in the context of successful cognitive aging.

POSTER 68

Functional connectivity in the healthy oldest old: Findings from the McKnight Brain Aging Registry

Visscher KM[6], Stewart, P[6], Sims SA[6], Bharadwaj PK[2], Franchetti MK[2], Rezaei RF[11,12], Merritt S[9], Jessup CJ[2], Raichlen DA[1], Porges EC[11,12], Geldmacher D[7], Hishaw GA[4], Alperin N[10], Trouard TP[5], Wadley VG[8], Levin BE[9], Woods AJ[11,12], Rundek T[9], Cohen RA[11,12], Alexander GE[2,3]

School of Anthropology[1] and Departments of Psychology[2], Psychiatry[3], Neurology[4], and Biomedical Engineering[5], University of Arizona and Evelyn F. McKnight Brain Institute, Tucson, AZ; Departments of Neurobiology[6] and Neurology[7] and Division of Gerontology, Geriatrics, and Palliative Care[8], University of Alabama at Birmingham School of Medicine and Evelyn F. McKnight Brain Institute, Birmingham, AL; Departments of Neurology[9] and Radiology and Biomedical Engineering[10], University of Miami Miller School of Medicine and Evelyn F. McKnight Brain Institute, Miami, FL; Department of Clinical and Health Psychology[11], College of Public Health and Health Professions and Center for Cognitive Aging and Memory[12], University of Florida and Evelyn F. and William L. McKnight Brain Institute, Gainesville, FL.

Abstract:

Measuring relationships among brain regions by using functional connectivity metrics has been a successful biomarker of disease, and has been shown to relate to cognitive function. The vast majority of this work has been performed in younger adults, and older populations with mean age well under 85. Little work has described functional connections in the oldest old.

There are two main benefits of characterizing functional connectivity in healthy oldest old individuals. First, it allows us to characterize what a healthy oldest old brain should look like, identifying typical distributions of functional connectivity metrics in the context of successful cognitive aging. Second, because these oldest old participants have many decades of divergent life experiences and relatively large variability on cognitive metrics, we can examine how variability in cognitive metrics relates to functional connections.

Data were acquired as part of the McKnight Brain Aging Registry, using methods harmonized across four sites at the University of Arizona, University of Alabama at Birmingham, University of Miami, and University of Florida. For this analysis, 62 community-dwelling, cognitively unimpaired older adults, ages 85 to 99 were included who had undergone Volumetric T1-weighted 3T MRI scans and 10 minutes of BOLD resting state data acquisition (TR = 3s) and for whom at least 100 timepoints met our strict quality control parameters. Cortical surfaces for each participant were determined using Freesurfer software (v6.0), and BOLD scans were pre-processed using Ciftify algorithms. All functional connectivity analyses were performed on the individual's cortical surface. Functional connectivity was measured within three well-characterized networks: Default Mode Network, Cingulo-Opercular Network, and Fronto-Parietal Network.

We found that this cohort of healthy oldest old participants showed strong, reproducible connectivity networks for the three standard networks we tested. Further, level of connectivity within the frontoparietal network was positively associated with scores on the MOCA, consistent with a contribution of cortical network integrity to performance on this test of generalized cognition. This work shows feasibility for examining connectivity in the healthy oldest old and helps set the stage for understanding how individual variability in connectivity relates to cognitive performance in this oldest old cohort.